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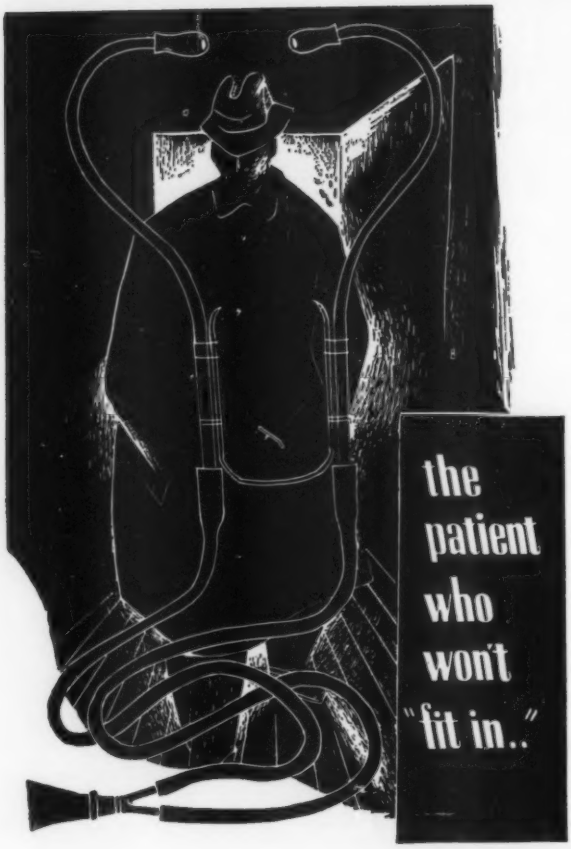
NEUROLOGY is published bimonthly at Minneapolis. Publication dates: January, March, May, July, September, November. Subscription rate: $8.00 a year, $1.50 a copy; outside U.S., $9.00 a year, $1.70 a copy. Louis M. Cohen, Publisher. Margaret M. Kane, Managing Editor. Maurice Wolff, Business Manager. NEUROLOGY, 84 South Tenth Street, Minneapolis 2, Minnesota.

ADVERTISING REPRESENTATIVES, NEW YORK 17: George Doyle, Lee Klemmer, Bernard A. Smiler, 50 East 42nd Street. Telephone: Murray Hill 2-8717. CHICAGO 6: Jay H. Herz, 20 North Wacker Drive, Suite 1921. Telephone: Central 6-4619. SAN FRANCISCO 4: Duncan A. Scott & Co., Mills Building. Telephone: Garfield 1-7950. LOS ANGELES 5: Duncan A. Scott & Co., 2978 Wilshire Boulevard. Telephone: Dunkirk 8-4151.



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INFORMATION FOR *Authors*

• NEUROLOGY, the official publication of the American Academy of Neurology, has been instituted to provide a medium for prompt publication of articles dealing with neurology and its cognate fields and to stimulate individual investigation in these various fields.

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Neurology

Problems in the Treatment of Bulbar Poliomyelitis

J. V. Monke, M.D., S. K. Shapiro, M.D. and A. B. Baker, M.D.

In the absence of specific antiviral therapy, the treatment of bulbar poliomyelitis resolves itself into supporting the patient while the disease process runs its course. It is impossible to predict whether a case will survive. Each one demands a maximum of treatment and effort on the part of the physician and nurse. Moribund cases may make dramatic recoveries when adequate vigorous supportive and therapeutic measures are instituted.

The general principles which apply to the management and treatment of acute bulbar poliomyelitis have been discussed in previous publications.[1, 2, 3] In specific cases, the practical application of these principles may require greater and more continuous expert medical and nursing care than is demanded by any other illness. A detailed consideration of some aspects of several cases of bulbar poliomyelitis may serve to emphasize the varied difficulties, medical complications and management problems which may arise.

REPORT OF CASES

Case 1.—A married woman aged 26 noted soreness and fatigue of the back muscles. Three days later her back was stiff, and weakness of the right arm and both legs was evident. The next day generalized weakness and difficulty in breathing developed.

From the division of neurology, University of Minnesota Medical School, Minneapolis.

Aided by a grant from the National Foundation for Infantile Paralysis.

Upon admission to the hospital on the fifth day, the patient had marked nuchal rigidity and resistance to straight leg raising. There was marked paresis of the extremities and diaphragm; the intercostal muscles were paralyzed, but accessory muscles of respiration were in use. A forced cough was barely audible. The patient could not void. The right biceps, right triceps, abdominal and both quadriceps reflexes were absent. The spinal fluid contained 90 neutrophiles and 30 mononuclear cells per cubic millimeter. The patient was placed in a respirator immediately. Prophylactic penicillin therapy, supportive intravenous infusions and continuous private nursing care were instituted.

On the seventh day the patient developed difficulty in swallowing. Subsequently the mucous secretions accumulated so rapidly that continuous pharyngeal suction failed to maintain an open airway. For this reason an immediate tracheotomy was performed, following which oxygen was administered through the positive pressure apparatus.[4] The patient became extremely apprehensive, and developed a fever of 104° F. on the eighth day. Trismus of the masseters made it impossible to open her mouth, and the pain about the right mandibular joint was distressing. The patient became disoriented, paranoid and developed auditory and visual hallucinations; this psychotic behavior persisted for the next six weeks.

On the sixteenth day of illness gastric feeding replaced intravenous infusions. A momentary crisis in which the patient suddenly became cyanotic and comatose developed during the evening of this day. This was relieved by aspiration of a plug of mucous which had obstructed the tracheotomy tube. The temperature remained elevated, and repeated physical examinations demonstrated the continuous presence of pulmonary involvement. On the seventeenth day intramuscular penicillin was reinforced with penicillin aerosol and intramuscular streptomycin. Oximetry on the twenty-second day showed that the patient could maintain adequate arterial oxygen saturation only with continuous oxygen therapy.

A sudden elevation of temperature to 105° F. on the twenty-fifth day and marked diminution of chest movements indicated the possibility of pulmonary atelectasis. A mucous plug was removed from the left main bronchus by bronchoscopy. The possibility of a pulmonary embolus was strongly considered. Three days later a thrombophlebitis developed in the patient's left leg. The limb was elevated and heat applied. The continued production of massive amounts of purulent foul-smelling sputum from the trachea and the persistence of pulmonary involvement during the next week suggested the presence of a pulmonary abscess.

Beginning about the thirty-fifth day the patient improved gradually. Four days later she was able to swallow liquids and soft foods, and the abnormal mental state cleared. By the fifty-sixth day penicillin and streptomycin were discontinued, the tracheotomy tube was plugged, and the patient began training in voluntary respiration. Her abilities and efforts were assessed by means of oximetry. On the sixty-seventh day, when the patient could remain out of the respirator eight minutes, the tracheotomy tube was removed. Two days later, her temperature rose to 104° F. and a roentgenogram demonstrated bronchopneumonia. Penicillin therapy was instituted again and the pneumonitis responded well. Ten days later the patient was able to breathe without aid of the respirator for 90 minutes, and six days later, for four hours. At this time the patient demonstrated marked emaciation. Respiratory movements were possible only through use of abdominal and accessory muscles of respiration. There was a bilateral paresis of the accessory nerve. There was absence of the reflexes in the right arm, the abdominal muscles, the knees and the left ankle. The right ankle reflex was decreased.

The arms, especially the right, were extremely paretic.

On the ninety-eighth day the patient was able to maintain herself out of the respirator for 10 hours, but it was not until five weeks later that she was able to sit upon the edge of the bed. Shortly thereafter she was able to stand alone. Complete freedom from dependency on the respirator was not achieved until five months after the onset of the illness. Subsequently, the patient spent much of her time in a wheel chair, and was soon transferred to a convalescent hospital for further muscle re-education and strengthening.

Reexamination of the patient 20 months after the onset of her illness demonstrated the presence of severe neurologic residuals. There was a droop of the left corner of the mouth and nasality of the voice. The musculature of the right shoulder girdle was paralyzed and markedly atrophic, and the muscles of the right upper and forearm were markedly paretic. Both lower extremities were paretic, the left more than the right. There was marked paresis of the muscles of the back with development of a double scoliosis. This had not changed since a previous examination three months before. Some weakness remained in the diaphragm, and the patient's ability to cough was slightly impaired. There was complete paralysis of the right and upper half of the left intercostal muscles. Deep respiratory movements were possible only through the use of hypertrophied accessory muscles of respiration. The right biceps and both patellar reflexes were absent; the right triceps and both Achilles reflexes were diminished.

In spite of these severe residuals, the patient moves about her house in a wheel chair and is able to walk if one hand is supported or if crutches are used. The patient can dress herself and accomplishes such manual tasks as knitting. She regularly aids in the preparation of meals. There is no mental deterioration, nor any change in personality structure. She is pleased with the progress she has made and looks toward the future with hopefulness.

Comment: This case demonstrates an unusually satisfactory recovery from an extremely prolonged and complicated case of poliomyelitis in which the brain and spinal cord were severely involved. The features of particular interest were the prolonged psychosis, severe tracheobronchitis, bronchopneumonia, pulmonary edema, atelectasis, probable pulmonary infarct and pulmonary abscess, thrombophlebitis and marked emaciation. This case not only demonstrates the difficulties which arise in the management of such an illness, but also brings into view the financial costs entailed in the maintenance and rehabilitation of some cases of bulbar

TABLE 1
BREAKDOWN OF COSTS IN TREATMENT OF CASE 1

Hospitalization, 156 days	$ 1,207.25
Hospitalization, convalescent hospital	538.00
Special nurses, 2,884 continuous hours	4,226.25
Oxygen and helium, 1,200 hours	2,927.25
Penicillin, 30,000,000 units	141.35
Streptomycin	450.00
Laboratory fees	115.75
Physical therapy	347.35
Miscellaneous (X-ray, surg. supplies, etc.)	95.15
TOTAL	$10,068.35

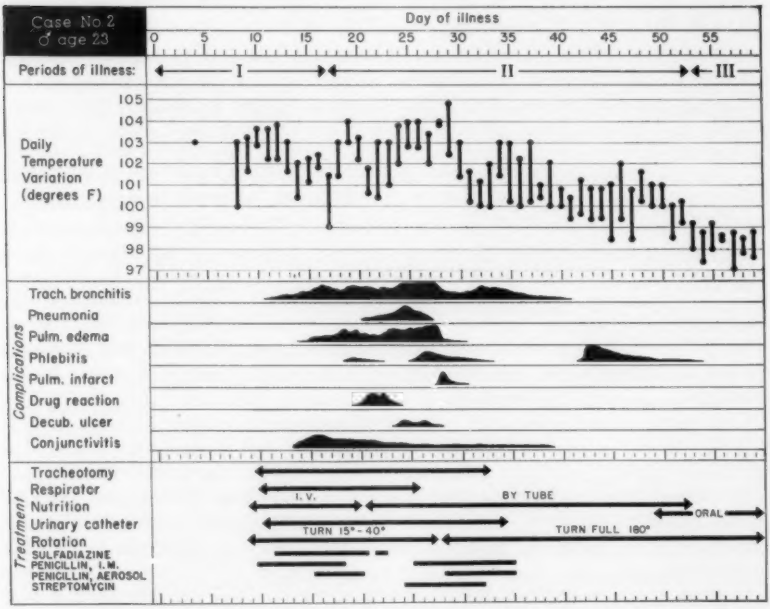
poliomyelitis. Table 1 presents the itemized costs involved in caring for this patient. The patient so afflicted can obtain unstinting amounts of medical treatment only through the pooling of the financial resources of a community. The reward for such extensive outlays of money and such prolonged numbers of man-hours is the return of a young mother to her home where, though somewhat handicapped, she can carry on her maternal duties.

Case 2.—A man aged 23 noted that he was listless and anorexic and had persistent left-sided headache. On the third day he experienced chills, fever, aching in the back and thighs, continued headache, a severe pharyngitis, a fever of 103° F. and mental confusion. The fifth morning, the patient noted difficulty in speaking and swallowing. The next day weakness of the legs, difficulty in focusing the eyes and periods of stupor developed. Paralysis progressed on the following day to include the left facial muscles, the neck flexors and the soft palate. On the eighth day, when the spinal fluid showed findings consistent with poliomyelitis, the patient was sent to the hospital.

Neurologic examination on the ninth day of illness revealed the following: The left pupil was dilated and did not react to light; the right pupil reacted sluggishly to light; there was a bilateral horizonal nystagmus; trismus and bilateral weakness of the masseter muscles were present; the left pterygoid and the left lower facial muscles were paretic; there was ptosis of the left upper lid; the left hypoglossal nerve was paralyzed and there was marked dysphagia; the voice was thick and hoarse, and the patient could cough only weakly; the left biceps and left triceps, the right patellar and ankle reflexes were diminished; the right abdominal reflexes fatigued rapidly; moderate nuchal rigidity was present and the Kernig's sign was positive; the sternocleidomastoid, infraspinatus, triceps, biceps on the right and the infraspinatus, pectoralis, deltoid, triceps, biceps and brachioradialis on the left were paretic; the extensors of the back were moderately weak and there was a mild paresis of the abdominal muscles. Re-examination of the spinal fluid showed 8 neutrophiles and 23 lymphocytes per cubic millimeter. Prophylactic penicillin, intravenous fluids, indwelling urinary catheter with prophylactic sulfadiazine, and continuous nursing care were begun.

Fever exceeded 103° F. through the thirteenth day of illness and then gradually subsided to normal on the eighteenth day. A tracheotomy was necessary at the end of the ninth day because the production of foamy sputum exceeded the ability to keep the pharynx suctioned. The patient was placed in a respirator on the eleventh day when respiratory difficulty developed. A 40 to 60 per cent oxygen mixture was delivered via the tracheotomy tube under 2 cm. hydrostatic pressure. On the twelfth day the patient's condition deteriorated; the temperature was 104° F., generalized muscle weakening appeared, and trismus of the masseters made suctioning of the pharynx difficult. The pulse varied between 120 and 130 per minute. Systolic and diastolic hypertension developed. From the thirteenth to seventeenth days a falling temperature curve was associated with mental and clinical improvement. However, prodromata of severe respiratory tract complications appeared on the fifteenth day when the patient had a chill and began producing increasing amounts of purulent tracheobronchial secretions. Oximetry studies on the next day showed the patient unable to maintain adequate arterial oxygen saturation for three minutes when unaided by 40 to 60 per cent oxygen and the respirator. On the eighteenth day the temperature rose to 104° F. The patient became irrational and restive, and severe headache and generalized body aches caused

much distress. Physical signs of pulmonary edema, inability to maintain arterial oxygen saturation when breathing room air, and edema of the eyelids and face were treated by reduction of intravenous infusions and administration of concentrated human albumin. Isuprel was given every four hours in an attempt to minimize bronchial constriction. Cultures of the tracheal secretions demonstrated an alpha hemolytic streptococcus and a penicillin insensitive Aerobacter aerogenes.



On the twenty-first day a purulent infection was noted about the tracheotomy wound. It responded slowly to applications of scarlet red and vaseline gauze. On the same day the patient developed giant hives. Penicillin was stopped and antihistamines given. When no improvement occurred, the sulfadiazine was also discontinued. Additional complications developed. The patient's color became dusky. Emaciation was evident. Superficial phlebitis of all available veins necessitated discontinuation of intravenous therapy. Throat and nose infections were massive. Alpha hemolytic streptococci were continuously present in the trachea, but the Aerobacter species was replaced with a Pseudomonas aeroginosa species. Bronchoscopy demonstrated much loose purulent material, especially in the left main bronchus. Roentgenograms showed bronchopneumonia. Oximetry demonstrated inability to maintain normal arterial oxygen saturation with inhalation of less than pure oxygen. On the twenty-sixth day a thrombophlebitis developed in the left leg. Tidal air on the following day was estimated to be less than one liter. Tracheal exudations required almost continuous suctioning. The patient's weight loss exceeded 50 pounds, and decubitus ulcers developed. Streptomycin was begun. A Levine tube was passed and attempts made to supply 3000 calories per

day in an effort to circumvent the intravenous infusions and combat the emaciation. Heparin and dicumarol therapy was initiated.

It was the opinion of the staff on the twenty-seventh day that the patient would succumb to his pulmonary affection. It was realized at this time that standard respiratory techniques could not combat adequately the dependent edema and hypostatic pneumonia which are a corollary of the supine position for many days. It was decided that the patient must be turned into the full lateral decubitus positions to secure adequate gravitational drainage of his diseased lungs. Achievement of such positions had hitherto been deemed impossible, especially when complicated by the facts that the patient's tracheotomy tube was connected to large diameter tubing of the positive pressure inhalation apparatus, the patient's vital capacity was under one liter, and his respiratory reserve, zero. A program of maneuvers was devised, and two persons trained themselves to detach the neckpiece from the respirator head, rotate the patient and reseal the neckpiece in rapid order. The patient was turned twice on the twenty-seventh day, twice on the following day and three times on the next day. Recovery was dramatic. His color improved, and on the afternoon of the twenty-eighth day the patient was able to maintain respiration voluntarily. To exploit the gravitational relationships of the pulmonary lobes even more, the patient was placed upright twice during the day to aid drainage of the upper lobes. On the next day he was transferred to a bed. A schedule was begun in which full right and left decubitus positions were alternated with half hour periods of high supine Trendelenburg positions. On the thirtieth day the patient coughed up much mucoid material. He began to turn himself in bed, showed interest in his surroundings, wanted a radio and compensated for his difficulty in speech by writing notes.

During the next ten days, the patient's temperature again showed variations ranging from 100° F. to 103° F. While undergoing anticoagulant treatment for phlebitis, he developed a slight chest pain on the thirty-second day. It was thought that a small pulmonary embolus had lodged. Proteus organisms were cultured from the urine for the first time. Repeated cultures of the trachea showed persistence of the Pseudonomas organisms found previously. It was noted that material suctioned from the trachea smelled of vanilla. Investigation revealed that the paresis of the patient's esophageal musculature was permitting backward flow of the 2000 calorie per liter egg nog from the stomach whenever the patient was placed in Trendelenburg position, while being fed through the nasogastric tube. Thereafter, he was fed only in the sitting position. It was difficult to assess the degree to which the patient's drug sensitivity contributed to the continued fever. Treatment evolved during this period included removal of the indwelling urinary catheter, withholding all antibiotics, performance of gastric feeding only with the patient in the sitting position, maintenance of 50 per cent relative humidity and 68° F. room temperature continually, greatly increased physical therapy, forced feedings of 7000 calories per day with 6 grams of protein per kilogram, and the use of oxygen by tracheal catheter whenever respiratory inadequacy demanded. On the thirty-seventh day the patient sat in a chair, wiped his mouth and coughed material from his trachea into his mouth. Thereafter the tracheotomy tube was closed.

Four days later he again developed thrombophlebitis. A new bout of fever continued for ten days. Anticoagulant therapy, ace bandages and elevation rapidly controlled this final difficulty. On the forty-eighth day the patient could swallow a thick gruel; the tracheotomy tube was removed. Five days later the patient stood for a few minutes, and soon after he began to walk with crutches. Solid food was taken regularly after the fifty-ninth day.

On the sixty-first day of illness the patient was transferred to a rehabilitation hospital. Neurologic examination demonstrated a mild paresis of the left facial muscles, nasal speech, marked emaciation and a generalized weakness which required him to use crutches. An electroencephalogram demonstrated low voltage waves of 2 to 7 per second interspersed with large waves suggestive of myoclonic movement but not diagnostic of it.

Comment: This case is of particular interest because of the dramatic results obtained from achieving degrees of gravitational drainage of the lungs hitherto considered dangerously impossible on a tracheotomized "iron lung" patient. As far as is known, frequent rotation of such a patient into the full lateral decubitus positions has not been reported previously. The attending staff believed that this measure alone was responsible for the patient's spectacular improvement from a moribund state.

Three stages of illness may be recognized during this patient's hospitalization. The first stage, extending through the seventeenth day, witnessed the rise and subsidence of the initial febrile response. Stage two encompassed a sequence of severe febrile and toxic periods ascribable to secondary complications of respirator-tracheotomy care. These relented on the fifty-first day. Stage three was a 10-day period occupied with convalescence to a point at which the patient was able to live in a rehabilitation center without continuous medical care.

Such a sequence of secondary complications as were encountered in this case, each as life-threatening as the original virus invasion, indicate the clinical challenge in the care of this type of patient. The pulmonary edema, bronchopneumonia, tracheobronchitis, thrombophlebitis, conjunctivitis, decubitus ulcers, tracheotomy infection, urinary tract infection, drug sensitivity and loss of weight in thirty days were complications which compounded the difficulties of supporting the patient's physiologic systems.

This case demonstrates that in order to achieve a substantial number of recoveries from bulbar poliomyelitis, it is mandatory that the patient be cared for by a closely knit, well integrated team of mechanically, physiologically, and medically minded nurses, neurologists, internists, physiologists and psychiatrists.

Case 3.—A woman aged 21, eight weeks postpartum, developed difficulty in swallowing. During the next 36 hours she noted nausea, headache, stiff neck, malaise and a fever of 104° F. At this time she was hospitalized. She showed dysphagia, moderate nasality of voice, slight rigidity of neck extensors, and a moderate bilateral paresis of the sternocleidomastoid, trapezius and deltoid muscles. The spinal fluid contained 69 neutrophiles and 7 lymphocytes per cubic millimeter.

Her temperature rose to 105° F. but responded well to intravenous sodium salicylate and to alcohol sponges. During the third day of illness apprehension, restlessness and disorientation, accompanied by signs of respiratory difficulty, developed and

respirator care was instituted. Prophylactic penicillin therapy was also begun. Impaired ability to swallow or expectorate the secretions pooling in the hypopharynx prevented maintenance of an adequate airway, and led to tracheotomy four hours later, followed by continuous use of the positive pressure oxygen apparatus. On the fifth day of illness paresis of the right arm and left leg developed. Her ability to maintain voluntarily normal arterial oxygen saturation as measured by the Millikin oximeter was reduced to five minutes.

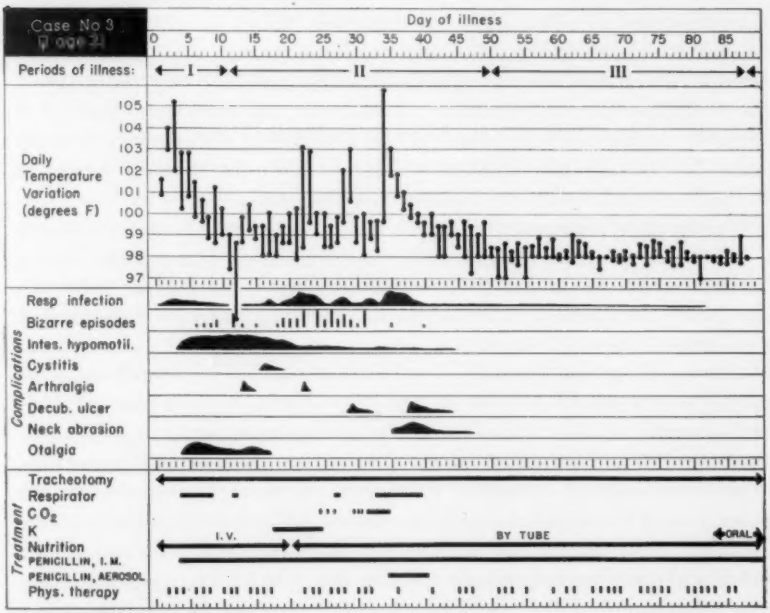
Fluid balance was maintained initially through intravenous infusions. On the eighth day a Levine tube was inserted and tests made of gastric emptying with measured amounts of tepid tap water. Watery vomiting with overflow into the trachea occurred on the next day. The patient's head was immediately turned to the side. Tracheal suction and repeated administration of 10 ml. portions of normal saline followed. Subsequently, a rigid schedule of pulmonary gravitational drainage was instituted by providing hour-long intervals of complete right and left lateral decubitus positions alternated with quarter hour intervals of high supine Trendelenburg positions. A two day elevation of fever with spikes of 103° F. accompanied this episode.

Electrolyte balance studies on the sixteenth day demonstrated slight dehydration and a hypopotassemia (K/3.4 meq). The latter was corrected by adding 1 to 2 gm. of KCl to each liter of intravenous infusions or 1 to 3 gm. to each liter of fluids administered by gavage. Bizarre spells indicative of marked dysfunction of the autonomic nervous system occurred. The disturbances followed no specific pattern but did reflect a predominant involvement of the respiratory center. A typical episode began with a sequence of apprehension, restlessness, labored respiration, drowsiness, lethargy and clouding of the sensorium. This was followed by alternate but irregular periods of shallow tachypnea, with the rate reaching as high as 45 per minute, and apnea. There were frequent evidences of carpopedal spasm, and occasionally there was rigidity of the limbs. The spells could usually be terminated by commands from the attendant to breathe slowly, by reassurance and/or by the administration of carbon dioxide. Usually the process ran its course in one to four hours. Subsequently the patient was sometimes tired and lethargic, but more relaxed, alert and cheerful. On several occasions she definitely experienced periods of hypoxia during which duskiness and cyanosis developed. At this time it was necessary to give artificial respiration and return her to the mechanical respirator. Following respiratory arrest on the thirty-fourth day the patient was kept in the respirator for a period of five days. From the thirty-ninth through the forty-third days the patient was kept on the respirator bed below the headpiece where she fared well. She was delivered into the respirator immediately whenever respiratory dysrhythmias developed. However, the majority of these episodes transpired without obvious cyanosis; frequently the nail beds and face were flushed and pink. Once, during the most severe period, episodes developed in modified form while the patient was in a respirator.

At various times additional bizarre disturbances were encountered: (1) epileptiform convulsions, hallucinations, clawing grasping movements and occasional emotional outburst of a hysterical nature; (2) a drop in body temperature to 95° F. rectally, and on another occasion a marked febrile over reaction with a sudden temperature rise of 106.2° F. following probable aspiration of small droplets of blood from tracheal trauma; (3) relative fasting hypoglycemia of 56 mg. per cent and relative fasting hyperglycemia of 320 mg. per cent; (4) blurring of vision, constriction of pupils, vertigo and paresthesias; (5) marked and frequent cardiac arrhythmias and

tachycardias and moderate fluctuations in blood pressure; (6) gastrointestinal hypermotility with peristaltic rushes causing fecal incontinence, and prolonged periods of hypomotility requiring Prostigmine injections to permit gavage; (7) urinary incontinence as well as urinary retention requiring indwelling catheter.

This same period of illness from the eleventh to the fiftieth days was marked also with five separate elevations of fever, during which the episodic instability of the autonomic nervous system tended to be more severe. On the day of highest fever neither bronchoscopy nor roentgenography demonstrated abnormalities in the chest, but until the fortieth day when the fever stopped, large quantities of purulent tracheal secretions were removed by suction.



The fiftieth through ninetieth days were restive, tedious ones marked with thrice daily nasogastric intubations performed by the patient herself. The autonomic aberrations gradually relented. The patient slowly became ambulatory using wheel chair and crutches. On the eighty-fourth day the patient swallowed a glass of tea. Thereafter, the ability to swallow liquid foods slowly returned. On the ninetieth day the patient was transferred to a convalescent hospital, where physiotherapeutic measures were directed to resolving joint stiffness and to re-education of the musculature. Swallowing adequate to permit nutrition without the use of the nasogastric tube did not develop until the one hundred and twentieth day. The patient was finally discharged 150 days after the onset of her illness. At this time the residuals consisted of moderate pharyngeal and laryngeal dysfunction, a marked left foot drop necessitating the use of crutches, and continued generalized weakness.

Comment: This illness is remarkable in that the patient survived such

profound dysfunctions of autonomic activity with eventual complete recovery. On the thirtieth day when respiratory episodes were occurring three to five times daily, the electroencephalogram demonstrated an abnormal rhythm with diffuse random low voltage waves of slow activity and evidence suggestive of lesions deep at the base of the brain. Follow-up study on the eighty-eighth day demonstrated a completely normal pattern. A Hunt-Minnesota Psychometric Test for evaluation of recent mental deterioration yielded a score two standard deviations from normal.

In retrospect, four stages of the illness can be distinguished: (1) rise and subsidence of a febrile period related to the onslaught of the virus through the eleventh day; (2) convalescence through a period in which deranged autonomic centers regained grossly normal activity and progress was complicated with secondary illness; (3) convalescence through a period in which partial control of the swallowing mechanisms was regained permitting the transfer of the patient; (4) rehabilitation of skeletal muscle function at a convalescent hospital.

The bouts of respiratory difficulty which this patient experienced were of particular interest. Many respiratory difficulties encountered during the first weeks resembled those of anxiety hyperventilation. The fact that the episodes were not relieved by oxygen administration, were present in modified form when the patient was in a respirator, and were diverted in their cyclic progression by use of carbon dioxide, indicated that the primary problem was not one of hypoxia, of pulmonary exchange or of cardiovascular dysfunction. The fact that during a severe episode oximetry studies demonstrated an inability to maintain arterial saturation on pure oxygen, but an ability to maintain a normal saturation in the presence of 3 to 10 per cent carbon dioxide, indicated that the primary deficiency involved the autonomic portion of the patient's respiratory center and that her respiratory mechanisms frequently depended solely upon stimulation of the chemical respiratory center. It is felt that the procedure instituted on the thirty-fourth day, namely keeping the patient lying on the respirator bed and receive continuous oxygen with immediate institution of mechanical control of respiration each time that periods of apnea occurred, is the procedure of choice in handling these disturbances in respiration. Oxygen administration is indicated to prevent the potential danger of hypoxia which may accompany the disturbances of respiration.

CONCLUSIONS

The medical problems of a patient with bulbar poliomyelitis present themselves in a sequence of three stages:

During the first stage the invasion of bulbar and higher autonomic nuclei of the brain by the virus removes the integrating control of the brain over many elements in the patient's various physiologic systems. The more continuously and adequately each of these systems receives artificial support from the physician and nurse, the more likely it is that the patient will survive into that period when the temporary derangement of the involved nerve cells ceases and normal functions return or are approximated.

If the patient survives the first stage, his course of illness blends into a second stage in which the physician and nurse must aid him to avoid or must help him through a variety of secondary illnesses to which he becomes subject by virtue of his debility and the physiologic abnormalities incident to tracheotomy. Knowledge on the part of the physician and nurse of the complications which may be expected often helps avoid them, or failing this, leads to prompt activation of therapeutic measures.

The third stage of the patient's illness is one in which the patient regains physical strength and rehabilitates himself within the limitations imposed upon him by the local pareses and paralyses which remain as residuals of his acute involvement. During this stage active physical therapy and rehabilitation are carried out.

To achieve survival of the patient through the first and second stages of illness is one of the most challenging, demanding and dramatic experiences the physician and nurse may encounter. To succeed in so specialized an undertaking as that of substituting for some of the autonomic controls of the patient's central nervous system requires devoted minute by minute attention and demands of the physician fivefold capabilities:

1). He must make an adequate neurologic evaluation of those portions of the patient's central nervous system affected by the virus and know what may be expected of such derangements, both immediately and subsequently.

2). He must have an excellent understanding of the normal interrelationships of the body's physiologic systems, and must have a knowledge of how deviations from normal function through loss of central nervous control may be checked and normalized by the use of physical and pharmacologic aids.

3). He must watch continuously for secondary illnesses which may complicate the primary one, and when recognized, must implement the already complicated care of the patient with immediate prophylaxis or maximum therapy.

4). Both physician and nurse have a well developed mechanical and technical skill. It is not an exaggeration to say that the over-all manage-

ment of a respirator sick room is a form of "mechanical medicine."

5). Finally, the staff must be capable of vigilance and patience which is measured minute by minute. Crises and moments of dramatic action are frequent and unannounced. Failure to survive may hinge upon momentary lapses of care. Probably nowhere in medicine is it any more true that "A patient does only as well as the total time devoted to him."

We advocate a "total push" form of physiologic support. If practices are indicated which by normal hospital routines are deemed to have risk, it is mandatory not to be conservative, but to guard in this way against the pitfalls of the procedure in question that the risk is minimized. When such thorough efforts to maintain the physiologic systems are coupled with prophylactic and therapeutic measures designed to forestall or treat the customary secondary illnesses, it would appear that many of the deaths of respirator-tracheotomy patients can be circumvented. The goal is one of avoiding all deaths except those which at autopsy show massive irrevocable destruction of the vital centers of the nervous system.

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• Although we admit the general proposition that the anterior roots of spinal nerves are motor, and the posterior are sensory, there is an apparent exception to this which has generally been admitted of late years.

When we divide the posterior root of a spinal nerve, all sensation is lost to the terminal branches of the mixed nerve of which it makes a part. So also is motion utterly lost by dividing the anterior root. If, however, the spine has been opened with certain precautions, and the nerve roots, after exposure, have been left at rest for a certain time, it will be found that distinct evidences of sensibility may be evoked by irritating the anterior root. Should we then divide this trunk, the central end will be found to possess no sensibility such as will exist in the peripheral extremity, and section of the posterior root will abolish altogether these evidences of feeling; so that it becomes clear that the fibres communicating sensation to the anterior root must depend upon the posterior root.

—S Weir Mitchell in *Injuries of Nerves and Their Consequences*, published in 1872.

Psychosomatic Aspects of Neurology

Roland P. Mackay, M.D

THE ADJECTIVE "psychosomatic" has been used so loosely in varying senses in recent years as to have little specific meaning. We hear it most commonly in the phrase "psychosomatic disorder" to indicate an abnormal condition with both mental and physical aspects. In some instances it seems to indicate only hysterical disturbances; in others, states of anxiety with perverted physiologic functions manifested as symptoms, such as tachycardia, visceral unrest, increased sweating, etc. Some physicians use the term to indicate the emotional effects seen in patients ill with ominous diseases.

Alexander insists that the term should be used only to describe a method of approach by which it is recognized that the living body is afflicted by a variety of disorders with both psychologic and physiologic aspects, and that a complete study of such disorders must include the psychologic as well as the physiologic approach. More specifically, the term, as used by Alexander, denotes that psychologic or emotional states induce, or are accompanied by, disturbances of the autonomic nervous system, which lead to symptoms of disordered function and hence to tissue destruction and even death. According to this concept, the psychosomatic study of the patient includes analysis of the personality and its psychologic peculiarities so as to explain the concomitant disorders of function and resultant destruction of tissue. Thus the patient's body may be injured physically, not only by organic conditions, but also by physiologic disturbances arising from disturbed emotional states. The psychosomatic approach, therefore, means simply a search for the psychogenesis of organic disease. However, if one adopts the holistic philosophy so vigorously urged by such authors as Alexander, French, Dunbar and others, by which man is considered as one and all his diseases as both mental and physical, the term ought also to include the search for the organic basis for mental states. We should then be seeking the causes,

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Read at the first biennial meeting of the American Academy of Neurology, French Lick, Indiana, June 3, 1949.

whatever they may be, mental or physical, for whatever disease we study. Unfortunately, nobody is doing this: nobody knows enough to do it adequately. The organicists seek organic bases for disease, and the psychoanalysts seek the mental causes for disease; neither knows enough of the other's field to operate skillfully, or even comfortably in it.

Accepting the definition of psychosomatic approach as the search for the psychogenesis of organic disease, what is there to say about the psychosomatic aspects of neurology? To what extent, and in what specific details, do mental states cause neurologic disease? This is a vast uninvestigated field through which we must pick our steps with the utmost care and circumspection, adhering rigidly to strict canons of intellectual integrity. Above all, we must not be prejudiced at the outset, and our minds must be kept open to whatever conclusions may seem inescapable. Accustomed as we are to recognizing that mental abnormalities may follow pathologic changes in tissue, we must likewise be ready, if the facts warrant it, to conclude that mental states may, through disordered function, lead to the injury or death of tissue.

At the outset, we must exclude certain specious and even trivial sequences, for example, the depressed patient who puts a bullet in his motor cortex, or even the erotic young man who contracts syphilis and develops general paresis. In a sense, these men suffer from neurologic disturbances as a result of their emotional states, but this is only incidental. In the first instance the patient obviously suffers from a mental disorder, the neurologic consequences being fortuitous, since he might have put the bullet in his heart or elsewhere, so that there is nothing specific in the sequence. In the second instance, the libidinous urge might merely have resulted in a pleasant evening, or in the pregnancy of his mate, or in syphilis with aortitis and no neurologic disorder at all. We have no evidence at all that the sexual urge leading to syphilis is in any way different from that leading to pregnancy, though certain emotional states might operate to determine the type of sexual exercise and hence the results. If there are any emotional factors that determine that a man with syphilis develops neurosyphilis rather than aortic syphilis, we know nothing of them. There is, however, no reason why the problem is not a legitimate one for study.

In the next place, we must admit that we know of no psychogenic factors which operate in such diseases as neoplasms, the degenerative neurologic diseases such as multiple sclerosis, amyotrophic lateral sclerosis, syringomyelia, Friedreich's ataxia and a host of others. Speculations as to the psychogenic factors underlying multiple sclerosis must at once be admitted to be gratuitous and founded upon no generally available body

of fact. That is not to say that such psychogenic factors may not at some future date be discovered and become generally recognized; they simply are as yet not known. A critical appraisal forces us to reject such fanciful and mystic forces as "the death wish" in the psychogenesis of neurologic disease, as well as the symbolic significance of the organ damaged.

The monumental work of Cannon and innumerable clinical observations, as for example in examinations for life insurance and for admission to the army, have indicated that acute emotional stress may often produce transient elevation of arterial blood pressure. Hypertension thus induced may result in neurologic damage through rupture of a congenital aneurysm or spasm and thrombosis of a cerebral blood vessel. Neurologic lesions occurring in this fashion must depend, in large part, on the chance location of the aneurysm or of the arterial spasm. There is inadequate evidence to convince us that chronic emotional states, such as anxiety, hostility, etc., lead to prolonged arterial hypertension, despite the testimony of psychoanalysts. If it is eventually proved that chronic arterial hypertension may result from emotional factors, the arterial degeneration, myocardial infarction and encephalopathy which follow in many cases may be considered psychic in origin. In that case, the psychosomatic aspects of neurology would include the hemiplegias, the pseudobulbar palsies, or the hemianopias and aphasias resulting from the emotionally induced chronic hypertension.

While considering such possibilities, one should mention hypothetical hormonal and endocrine imbalances as a result of emotional states. It is certain that fear and rage cause an out-pouring of epinephrine, and it is reasonably probable that they also stimulate the thyroid gland to increased function. What other endocrine effects they may produce can only be surmised. Emotional amenorrhea and dysmenorrhea are not strange ideas to us. Perhaps other effects may occur in the hypophysis, in the gonads and not unlikely in the islets of Langerhans, which could conceivably influence the nervous system in a deleterious fashion.

There are, however, neurologic conditions which certainly result, at least in part, from emotional or psychological factors. Some of the more important of these are described, and possible fruitful lines of further study are indicated.

MIGRAINE

For many years it has been recognized that migraine is a paroxysmal pathophysiologic disorder of the nervous system which, if it does not lead to structural changes in tissues, at least involves reversible changes in the brain. Migraine has an inherited, familial constitutional basis which

in effect consists in the tendency to respond to adequate stimuli with the unique physiologic changes of a migraine attack. People who lack this inherited pattern never have migraine, no matter what the provocation, although they may exhibit other patterns of disorder. Included in this inherited constitutional basis is a psychologic type, or profile, which is frequently observed in patients with migraine—high intelligence, quick perceptions, intensity of emotional reactions, a conscientious devotion to duty and to standards of excellence, sensitivity to the opinions of others and a tendency to doubt their own abilities—hence anxiety. One may well doubt whether this psychologic profile is indeed inherited, or whether it is acquired during the plastic years of immaturity under the impact of manifold personal relations. In any case, it exists often as a part of the foundation of migraine.

The psychosomatic aspects of migraine can scarcely be doubted. It is the experience of neurologists generally that emotional factors often precipitate attacks. Persons with the constitutional tendency frequently suffer attacks when subject to conflicting emotional attitudes, such as the need to compromise their standards in the face of excessive demands for work, or the need to express hostility despite their need for approval. The situation resembles that of the conditioned-reflex animal, forced to respond to urgent but conflicting stimuli. For the patient with the migraine constitution, such a situation involves an intensification of emotional response, which is expressed physiologically by excessive autonomic (perhaps largely sympathetic) outflow, with vasoconstriction and fatigue, and probably other pronounced physiologic changes.

THE ANXIETY HEADACHE

Many patients not subject to migraine suffer nevertheless from a rather stereotyped form of headache with which every neurologist and psychiatrist is familiar, and which we may call the "anxiety headache." The patient complains of a pressure on the vertex, or a tight band around the temples, or a heavy weight in the occiput and neck. Often it is an occipitonuchal ache. It may exist for months or even years without intermission, one of the chief features by which it differs from migraine.

Whether there is a constitutional physiologic basis for this headache is doubtful, but that it is largely caused by psychologic factors cannot be questioned. Relying again on a general clinical impression, it seems that such patients are the victims of chronic unremitting anxiety. For them, life is constantly "too much," or they are faced with a chronically insuperable problem of adjustment—for example, the passive man who must be aggressive, or the woman who cannot accept her femininity but

must live as wife and mother. In such cases there are variations in the degree of their inner stress, depending on the shifting pressures of life, so that their anxiety headaches may disappear and reappear over longer or shorter intervals.

What the physiologic disorder is in these cases can only be surmised, since no physiologic studies have been made to settle the matter. One may imagine increased muscular tension in the neck leading to a sense of weight of the head, or similar muscular tension in the occipitofrontal muscle, but without accurate studies no opinion can be formed.

PSYCHOGENIC BACKACHE

A closely related condition is the backache so often encountered in patients who make the rounds of neurologists, internists and orthopedists, and in whom no physical disorder can ever be found. From clinical experience one feels sure that these persons suffer from chronic emotional tensions and consequent fatigue. Undoubtedly, tensions arise from the conflicts between irreconcilable drives or between the demands of life and the inadequate emotional resources of the individual. Such patients, through fatigue, suffer a relaxation of the muscular support of the trunk and pelvic girdle, throwing the weight of posture and carriage on ligamentous structures with resulting aching pain. Often the pain may be relieved by belts and corsets, but a more radical cure might be effected by a resolution of the stresses of emotional adjustment, a difficult and tedious process requiring great rapport and personal empathy between physician and patient. Such patients must feel adequate to their life situations or overcome their conflicts between opposing emotional drives in order to recover from the fatigue underlying their symptoms. Again, we speculate in the absence of fact.

EPILEPSY

This is not the place to discuss the great problem of the cause of epilepsy. It should be stated at the outset that cryptogenic epilepsy, if it has a single cause, results from subtle derangements of the metabolism of the neurone, derangements far removed from purely psychologic factors and probably inborn as a constitutional trait. The electroencephalogram enables us to uncover these derangements even in the absence of clinical seizures. It is known that emotional factors frequently precipitate individual seizures. However, these factors cannot be considered the cause of epilepsy; they simply serve as a trigger mechanism to a condition already present.

The case is cited of a 16 year old boy with a tumor of the brain who,

unexpectedly overhearing the doctor tell his father of the nature and seriousness of his disease, fell in a seizure on the floor. Again, there is the case of a married woman with epilepsy in whom the playing of classical music nearly always induced seizures, as demonstrated repeatedly both clinically and electroencephalographically. That this was an emotional rather than a simple auditory stimulus was shown by the fact that light jazz music or classical music of a gay or lilting type had no effect, while soft sentimental or romantic music nearly always induced seizures.

The psychomotor type of seizures, or epileptic automatisms, present a peculiar problem in regard to emotional precipitants. In such cases the attacks are not convulsions but complicated, inappropriate bits of behavior carried out during obtunded conscious states, frequently highly colored by emotional expression. Often such briefly dazed patients attack their relatives or others nearby, fly into rages or commit other acts of violence. Furthermore, they are notoriously unstable emotionally between attacks. One patient, a young married woman, was, even at best, an unpredictable, impulsive, erratic and erotic individual, either greatly in love with her husband or greatly at odds with him, subject to the strangest whims, and by turns cooperative and uncooperative with her physician. She had frequent psychomotor attacks in which she committed minor nuisances; broke dishes; lay down, dazed, on the doctor's couch, lifting her dress and holding her feet in the air. Such attacks lasted only a few moments, left no traces of memory and embarrassed her acutely. The electroencephalogram revealed a slow wave focus and psychomotor seizure focus in the left anterior temporal region, but all other neurologic studies gave normal results. The impression was inescapable that her unhappy marriage induced frequent attacks. Simultaneous divorce and administration of Paradione nearly eliminated her seizures. She remains a more even tempered and tolerant, though still unstable person, with rare psychomotor attacks. The drug has helped; it seems certain the divorce has reduced the psychogenic precipitation of her attacks. To understand such cases taxes the wisest clinician: cause and effect are inextricably confused; psychogenesis and organogenesis impossible to separate.

Apart from these puzzling psychomotor epileptic cases, the role played by emotional factors in ordinary cryptogenic epilepsy is largely unknown. What the chain of events is, from "psyche to soma," or, neurologically stated, from affect to effect, or vice versa, no one can say. The psychologic studies of adequate precipitating factors have never been made; the physiologic changes induced by these factors are quite unknown. This is

a field for some future researcher, with a mind broad enough to encompass both neurology and psychiatry, to explore and cultivate.

NARCOLEPSY

The twin symptoms of paroxysmal somnolence and emotionally induced tonelessness which constitute the syndrome of narcolepsy offer a challenge to the psychosomatic method. It is well known that the syndrome may result from organic disease in the hypothalamus, and yet the role played by emotional stimuli is an intimate part of the clinical picture. These patients may fall asleep irresistibly under even the most exciting circumstances, yet they are more apt to do so when emotional stimulation is minimal and the setting monotonous. Under abrupt and unexpected emotional excitement, such as sudden laughter, acute startle, even keen gratitude, they fall helpless, with toneless skeletal muscles and absence of tendon reflexes. From a psychosomatic standpoint, this is most intriguing. Both normal and narcoleptic sleep are facilitated by monotony and lack of emotional stimulation, while cataplexy is induced by abrupt emotional stress, but the physiologic mechanism is largely unknown to us. It is evident that the neural correlates of emotional states act through hypothalamic connections to make vivid the activities of the cerebral cortex, while the absence of emotional stimulation, again acting upon hypothalamic neural structures, induces that widespread cortical inhibition which we call sleep. In narcolepsy, as in migraine and epilepsy, the emotional factor is merely a precipitating agent, acting upon an organically disordered neural mechanism for the production of symptoms. Here again is work for the neurologist of the future. If we understood these things we should open the door to many mysteries.

ACCIDENT-PRONENESS

Industrial engineers are aware of the fact that certain persons exhibit a preternatural proneness to accident. Experience with such persons is rather limited, but it seems that they must suffer from an emotional structure which interferes with their orderly motor activity. The "death instinct" of Freud is dubious in explaining their constant tendency to accidents which endanger their life and limb. Their difficulty seems to be a general and not a specific one—an emotional intensity which causes them to plunge at what they do, and to be unrestrained by the calm caution which protects their more careful fellows. These persons do not unconsciously wish to be hurt, or to castrate themselves symbolically, or to achieve some mysterious advantage in their personal lives. They simply approach life with such reckless eagerness that their caution never wakes

up in time. As a result, their movements are too quick and ungoverned to be smoothly restrained, and their purposes too impulsive to be censored by forethought. Perhaps these people represent a psychosomatic problem in the field of neurology which we should take into account.

CONCLUSIONS

In all these conditions it is evident that our knowledge is deficient in two wide areas. We need, first, more precise information as to the nature and quality of the emotional stimulus in each instance. We need to know just what emotional dynamics lie back of the attacks of migraine, backache, epilepsy, etc., and we need to know the exact degree to which emotion may be effective in inducing such attacks. In the second place, and more importantly, we must understand the nature and quality of the physiologic disturbance which underlies the emotion. They are very largely unknown, and they must be learned before we can understand clearly the psychosomatic aspects of these conditions.

Thus it would seem that the psychosomatic aspects of neurology offer a most urgent problem for the neurologist. Too long have neurologists exercised themselves over details of the end stages of organic disease. It is the proper concern of the neurologist to invade the broad field of the dynamics of autonomic function. To rescue a huge group of neurologic disorders he must give attention to the intimate details of visceral and hormonal behavior which he has so long ignored. As the dynamic psychiatrist has passed beyond the descriptive formulations of Kraeplin to the study of the patient's mind in action, so the dynamic neurologist of the future must leave his static concepts and busy himself with the autonomic nervous system in action.

> In the following work I have endeavored to present a Treatise on Diseases of the Nervous System, which, without being superficial, would be concise and explicit, and which, while making no claim to being exhaustive, would nevertheless be sufficiently complete for the instruction and guidance of those who might be disposed to seek information from its pages. How far I have been successful will soon be determined by the judgment of those more competent than myself to form an unbiassed opinion.
>
> One feature I may, however, with justice claim for this work, and that is, that it rests to a great extent on my own observation and experience, and is therefore no mere compilation. The reader will readily perceive that I have views of my own on every disease considered, and that I have not hesitated to express them.
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> —William A. Hammond in *A Treatise of Diseases of the Nervous System*, published in 1871.

On Certain Aspects of the Sensory Organization of the Human Brain

II. A Study of Rostral Dominance in Children

Robert Cohn, M.D

BENDER and his associates,[1, 2] and this author and his associate,[3] have shown independently that, under certain conditions of brain function, only the more rostral of two simultaneously applied ipsilateral cutaneous tactile stimuli was perceived. Each of these studies was made primarily in adult populations. The basic condition for the observed dissolution of perceptual organization was the presence of irreversible changes in the central nervous apparatus, primarily in the thalamoparietal projection system. The basic pattern of clinical response was that a tactile stimulus to the face, particularly to the nose or lip, obliterated all more caudal simultaneously applied tactile stimuli; a shoulder stimulus obliterated a simultaneously applied elbow, wrist or hand stimulus. Light tactile stimuli were ordinarily utilized, but pin prick gave grossly similar results. In the lower limbs, the hip stimulus obliterated perception of the simultaneously applied knee or ankle touch. The gradients of perception in other body structures such as the hip versus hand, chest parts, or pelvic parts, etc., were not nearly as precise or reproducible as in the face and upper limb elements.

Over a recent eight-month interval approximately 50 essentially normal children between the ages of three and ten years of age were examined for evidence of rostral dominance. The subjects were normal with respect to their sensory apparatus as determined by responses to disparate single cutaneous stimuli. Many of the children were examined because of various paroxysmal disturbances in behavior or losses of consciousness. A large number of the children just innocently accompanied their parents who were under study. The remarkable finding was that nearly all the children between the ages of three and five and a half years showed persistent patterns of response that in all ways resembled the picture observed in adults with irreversibly disturbed brain cell activity. With each

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child it was necessary, of course, to make friends in order to gain his confidence, attention and strict cooperation. Precautions were taken and allowances made for the child's tendency to "please" the examiner. In nearly all cases the observer requested that the eyelids remain closed during the examination. Often, and repeatedly, during the testing the observer would not stimulate the patient in any part of the body and would ask, "Where did I touch you?" If the child indicated, as was frequently the case, a point or points of stimulation, it was found expedient to stop the examination for a short time, and then resume testing. In detailed work, because of these interruptions, the examinations often consumed more than an hour. A single case is presented as a paradigm of the entire series.

CASE PRESENTATION

K. O., aged four and one-half years, was bright, alert and friendly. The child was referred for neurologic and electroencephalographic study because of three episodes of unconsciousness. The first attack had occurred about nine months previously when the patient was thwarted by a playmate from going down a slide. At that time she cried, then stiffened and fell to the ground. The mother indicated that the child's eyes rolled up into her head and that the lips were blue and the hands cold. The mother also stated that the child was unresponsive to any stimuli and that she remained in this condition for a long time. Following this spell the child was sleepy. At no time was there incontinence. She did not injure her tongue. She had two additional clinical episodes, under similar maladaptive stresses. There was no history of febrile convulsions, and no familial history of convulsive disorders.

On examination she stood and walked well. The Romberg test was negative. Detailed examination revealed no gross disturbance in any pair of cranial nerves. The torso was symmetric and well formed. Upper and lower extremities showed normal muscle volume and strength, as well as normal range and accuracy of movement.

The patient had a nice knowledge of body parts, as evidenced in her drawing of a man and in her responses to requests to point to her nose, ears, etc. There was a well organized right-left orientation. She was even able to print certain letters of the alphabet and to copy relatively complex geometric figures.

In careful, cutaneous sensory, single stimuli testing all responses were appropriate and accurately localized. She even responded to dermal number writing when only the numbers zero and one were utilized. Her adaptation and persistence times to pin prick also were within normal limits. All posterior column functions appeared intact.

Ipsilateral simultaneous cutaneous stimulation of the cheek and hand resulted in the perception of only the face stimulus on the proper side. When told that she really was touched in two places she pointed to the other cheek. Similar responses were noted in all other parts tested. Namely, if the hand and shoulder were stimulated simultaneously she only perceived the shoulder stimulus; and if pushed for a second point, she projected it to the opposite shoulder. If the left shoulder and the right hand were stimulated, again only the left shoulder stimulus was recognized. The hips in this patient dominated the hand and elbow, but not the shoulder. The hip obliterated all more caudal simul-

taneously applied stimuli placed over the lower extremity. In this patient simultaneously applied hand and ankle stimuli were properly recognized repeatedly as two distinct points of stimulation.

DISCUSSION

Nearly all the patients comprising this series showed a pattern of response similar to that described above. Frequently, certain elements in a given individual were properly resolved, such as the hand and ankle in the presented case, but in the statistical ensemble the overwhelming pattern was that of rostral dominance within the prescribed limits set forth. Instead of the term rostral it might be more exact to speak of a proximal dominance with the head being considered as the most proximal element of the body. This concept is particularly interesting in that, in discussing the findings with certain adults who had displayed rostral dominance, some had indicated that, "Well, my hip is closer to me than my foot!"

The phenomenon of displacement of the more caudal or distal stimulus to the homologous symmetric rostral body part has been most clearly detailed by Bender and his associates.[2] Their study was carried out on a series of adults who had irreversible lesions of the brain.

At times the children in this series were asked specifically whether they felt one or two stimuli; in the majority of cases they said only one, but when two stimuli were admitted, they repeatedly could, or would, only localize correctly the rostral stimulus. The second stimulus was frequently displaced to the homologous body part, or at times the patient simply stated "I don't know."

Occasionally, either inadvertently or as a planned part of the experiment, the child was allowed to keep the eyelids open. In the younger age group, the proximal stimulus, especially in the face and upper limb combinations, was perceived alone. This occurred even when the stimuli were applied with moderate slowness. Similar observations have been made in certain adults with local or general brain pathology.

At the critical age of approximately six years in the grossly normal child, the pattern of rostral, or proximal, dominance is no longer evident; or it is evoked only (as in the normal adult) in the first or second pairs of stimulation. I have found this to be a fairly acceptable test of "backwardness" in children. A persistence of the phenomenon of rostral dominance in a well-developed child past the age of six years has proved to be fair evidence of mental retardation.

From these results it is obvious that there is an innate pattern of perception of multiple simultaneously applied ipsilateral cutaneous stimuli. When the phenomenon is observed in the adult as part of a disease process,

it represents a regression to a more primitive level of perception and adaptation. Moreover these results indicate that sentiency to, and the resolution of, multiple disparate cutaneous stimuli is a learned process, and that the apparatus necessary for this learning develops and is utilizable for this purpose at the approximate age of six years in the normal individual.

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• The aesthesiometer is an instrument for the purpose of determining the degree of tactile sensibility possessed by the patient. The instrument was devised in 1858 by Dr. Sieveking, of London. Its value in cases of aberrations of sensibility depends upon the fact, ascertained by Dr. E. H. Weber, that the capability of distinguishing two impressions made upon the skin simultaneously, varies in different regions of the body according to the distance they are apart. In sensitive regions, as the end of the finger, the two points of a pair of dividers can be distinguished at about the twelfth of an inch apart, while in the middle of the back only one point is felt, though they are two inches apart. In accordance with this principle, the aesthesiometer is used to determine the sensibility of the skin in various diseases, it being well known that this is subject to variation.

Thus when the sensibility is intact, two points, touching the back of the hand at the same time, can be distinguished as two points when separated an inch. If, in examining a patient, we should find that, when the two points were two inches apart, the patient felt but a single impression, we should know that he had lost sensibility in the cutaneous nerves of that part of the body.

In 1861 I described an aesthesiometer which I believe was the first used in this country. It consisted of a pair of dividers, to one arm of which the arc of a circle, in brass, was affixed. This arc was divided so as to measure tenths of an inch. A short time since, I suggested to Mr. Stohlman, the instrument-maker, a modification of this instrument, which for convenience is, I think, superior to all others.

—William A. Hammond in *A Treatise of Diseases of the Nervous System*, published in 1871.

Benadryl in the Treatment of Parkinson's Disease

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BUDNITZ,[1] in June, 1948, released a preliminary report concerning eight patients suffering from Parkinson's disease who were treated with Benadryl (b-dimethylaminoethyl benzhydryl ether hydrochloride). He observed that "all of them in the arteriosclerotic group were treated with Benadryl over a period varying from 3 to 14 months. All patients noted considerable improvement in the symptoms so long as the drug was administered. Four of the treated patients continued to use parasympathetic inhibitory drugs of the atropine series, and there seemed to be a synergystic action between these drugs and Benadryl."

With this encouraging note regarding a disorder which has long resisted therapeutic attack, the present study was begun in July 1948. Keeping in mind the early enthusiasms built upon the reaction of parkinsonian patients to the numerous drugs which have been introduced from time to time, and the subsequent discouragement aroused by the gradual waning of effectiveness of these drugs, objectivity has been closely observed in this study. This detachment is necessary at this time since a number of new drugs (Parpanit,[2] Diparcol,[3] Tolserol (myanesin),[4] Artane and several antihistaminics) are being advocated in the treatment of Parkinson's disease.

CASE MATERIAL

Thirty-five patients comprise this study. Of these, seven were in a hospital and had been institutionalized for a period varying from one to 27 years. Three of these patients were bedridden due to pronounced flexor rigidity and inability to move limbs or body, and they required spoon feeding. They presented very advanced forms of postencephalitic Parkinson's disease. The 28 remaining patients were drawn from private practice, and three of these were bedridden. The duration of illness varied from two to 29 years. Half of the cases were between five to ten years'

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Read at the first biennial meeting of the American Academy of Neurology, French Lick, Indiana, June 1, 1949. Revised for publication at this time.

duration, and the great majority were between two to ten years' duration. Five patients were in the 20 to 25 year period, and one patient had had the disease for 29 years. Twenty patients were considered postencephalitic, 12 were of the idiopathic type, and three were of the arteriosclerotic type of Parkinson's disease. One 50 year old male had had a cervical tractotomy performed with resultant left hemiplegia. Treatment was given to this patient in an effort to influence the rigidity and tremor of the right side of the body. Patients in this series received Benadryl therapy from 2 to 11 months. The youngest patient was 29 years of age, and the oldest 70. Careful histories were obtained and complete neurologic examinations carried out in every case. Hematologic studies were done before and during treatment in order to determine whether there were any untoward effects resulting from use of the drug. As in previously reported studies of the use of Benadryl for the treatment of allergic disorders,[5] no abnormal laboratory findings were revealed during treatment in this series. Each patient had received during the course of illness one or several of the various members of the belladonna group, synthetic antispasmodics and a wide variety of other preparations which have thus far been tried in the treatment of Parkinson's disease.

METHOD OF TREATMENT

Patients were observed for a period of at least one week, and in many cases had been under observation for years, so that a norm of their pre-Benadryl days of treatment was established. In order to score the results in as objective a manner as possible, it was necessary to eliminate or temper the rather prevalent factors of wishful enthusiasm in those attempting the use of a new drug, or the cynical attitude of futility observed in some patients and their families. The effect of treatment upon the various symptoms and signs was calculated from data obtained from relatives, the supervising nurse, the attending resident, the examiner and, lastly, the subjective evidence as given by the patient himself. The latter data was scored only if it coincided with the material obtained from objective observers. Relatives and friends of patients who had been through successive periods of disillusionment and discouragement have a tendency to assess gains conservatively. Scoring was based on the following observable and subjective features: (1) tremor; (2) rigidity; (3) posture and gait; (4) ease of movement with respect to both gross movements, such as putting on of clothes and driving a car, and the various fine movements, such as handwriting, buttoning of shirt and vest,

Seven of the cases reported here were from the Moss Home, Jewish Hospital, Philadelphia.

etc.; (5) speech; (6) improvement of morale and alertness; (7) appetite and weight gain; (8) effect upon oculogyric crisis and other postencephalitic phenomena; (9) effect of substitution of Benadryl with placebos; (10) subjective feeling of well-being and improvement. The various methods of examining parkinsonian phenomena in order to evaluate the patient's response to treatment are commonly known, and need not be repeated here.

The patients were instructed to continue with whatever preparation they had been receiving, and in addition were given Benadryl in 50 mg. capsules four times daily, as had been suggested by Budnitz.[1] This regimen was maintained for a period of one week, and the response to treatment was noted by members of the family, friends, nurses, the resident and the examiner. Subsequently, Benadryl was administered alone or with hyoscine hydrobromide or Rabellon. One group of patients was then given the drug in increasing doses until the total was six to ten capsules per day. In another group the drug was diminished so that patients received three, then two, then one capsule per day. In those patients who responded favorably, it was found that the optimum salutary dose was from four to six capsules per day. Less than three capsules per day failed to produce a satisfactory effect. More than six capsules per day offered no further improvement in those patients who were definitely improved with four to six capsules daily. Those patients having a severe form of the disorder were given Benadryl hydrochloride, 30 to 40 mg., either intravenously or intramuscularly twice weekly, in addition to oral therapy. The patients not in a hospital who received Benadryl parenterally were given the drug intramuscularly by a member of the family who was instructed in this procedure. Six patients were given Benadryl alone orally after the belladonna derivative had been gradually withdrawn. During administration of Benadryl by the oral route alone, it was noted that there was an increase of tremor and rigidity. When the belladonna derivative was replaced, a greater degree of relaxation and lessening of tremor and rigidity were noted. The adjunctive drugs employed in the series were hyoscine hydrobromide in doses varying from 0.3 mg. to 0.8 mg., three or four times daily, and Rabellon, one-half tablet to one tablet four times daily. These two preparations were most effective when administered with Benadryl. In patients in whom drowsiness was produced with the use of Benadryl, or in whom drowsiness or somnolence was part of the clinical manifestations of the disorder, Amphetamine was administered in 5 mg. doses at 8 a.m. and 12 noon with satisfactory results. In a group of these patients Benadryl was withdrawn abruptly and replaced with placebos, but no alarming effects were experienced. How-

ever, there was a very rapid and noticeable regression to the former level of performance, and in some cases they were distinctly worse.

RESULTS

None of the patients to whom Benadryl alone was administered orally showed beneficial effects comparable to the use of the various belladonna derivatives. When Benadryl hydrochloride was administered either intravenously or intramuscularly, in 30 to 40 mg. doses, there was a very rapid effect with diminution or complete elimination of tremor and profound effect upon rigidity. This lasted for approximately three to six hours, and the patient felt relaxed for as long as two days thereafter. Intravenous doses of 50 to 60 mg. of Benadryl hydrochloride produced lassitude, marked muscular relaxation, drowsiness and difficulty in locomotion. These effects lasted for one-half hour to as much as two hours, following which the patient had a feeling of well-being, muscular relaxation and distinct lessening of rigidity and tremor. The most striking effect was achieved when Benadryl was used in conjunction with hyoscine hydrobromide or Rabellon. In many cases this was quite dramatic and appeared within the first 24 to 48 hours after treatment was begun.

Using the ten features enumerated in the method of treatment, scoring for each case was done by indicating a plus, plus-minus or zero for each item. The score of 8 was considered marked improvement, from 5 to 8 fair improvement, and any score under 5 was considered unimproved, since the factor of error, particularly in this disorder, would render a value of less than 5 statistically invalid.

The combined use of drugs showed marked improvement in 18 patients, fair improvement in 10 patients, or a total of improved patients comprising 80 per cent of the series. Seven, or 20 per cent of the total series, had scores of less than 5, and hence were considered unimproved. None of the patients was made worse during combined treatment. Among the seven patients designated as unimproved, two who were in the arteriosclerotic category did show improvement in the sense of well-being, and occasionally evinced improvement in rigidity.

Of the 20 postencephalitic parkinsonian patients, three who were bedridden showed no improvement. Three arteriosclerotic parkinsonian patients scored less than 5, and hence were included in the unimproved group. The remaining patient in the latter group was a case of idiopathic Parkinson's disease.

Tremor was perhaps the one feature which was most resistant to the effect of combined Benadryl therapy. Severe tremors were influenced only moderately, whereas mild tremors occurring mainly in one hand or one

limb were strikingly improved, and in some cases, were almost completely abolished. Rigidity was lessened almost uniformly, and the degree of relaxation allowed a very evident improvement in posture and gait, and likewise provided the release necessary for improvement in both gross and fine movements. Among the 80 per cent of improved patients were many who for the first time in years were able to clothe themselves unassisted, tie their ties, button vests, close safety pins and the like. Handwriting was improved considerably in the majority of this group, and speech was likewise improved. Several patients who formerly were unable to speak, or whose speech was inaudible, became capable of speaking and being readily understood. In the improved group the morale was heightened, and there was a distinct increase in alertness, initiative and work capacity. Increase of appetite and weight gain were observed in most of the patients comprising the improved group. Those individuals who had shown improvement regressed rapidly within 24 to 36 hours after substitution of Benadryl by placebo capsules, but regained improvement when Benadryl was given again. In the one patient showing frequent oculogyric crises, treatment lessened the crises at the outset, but did not eliminate them. Benadryl hydrochloride given intravenously or intramuscularly diminished the severity of an oculogyric crisis, but could not abort it. All of the improved patients had a feeling of well-being, and they were consistently aware of improvement.

In the main, Benadryl was found to be practically devoid of the distressing side effects so commonly observed with various atropine-like drugs used previously. In some patients, it was found that the dosage of hyoscine or Rabellon could be reduced slightly to overcome the effects of dryness of the mouth, mydriasis and the accompanying visual disturbances. The only problem encountered with Benadryl was drowsiness which appeared in about 25 per cent of patients. Most of them were able to adjust to this during the first week or two, and subsequently this was of little importance. Where drowsiness was pronounced, however, the use of 5 mg. of Amphetamine upon arising and at noon eliminated this reaction quickly. No drug dermatitis of Benadryl origin was encountered in this study.

Among five recent cases not included in the original series, one patient did show an unusual degree of reactivity to Benadryl. After one 50 mg. capsule she became extremely dizzy, drowsy, had a marked loss of appetite and remained apathetic for the greater part of one day. However, when she was subsequently given small doses of Benadryl and hyoscine she was finally able to tolerate, by ascending doses, 35 mg. of Benadryl and 0.3 mg. of hyoscine four times a day, and now is doing very well.

Of the other preparations which have been used, Pyribenzamine, Thephorin, Tolserol and Diparcol have for the most part proved ineffectual, and in the case of Tolserol and Diparcol some of the side effects have been so serious as to require immediate cessation of treatment.

REPRESENTATIVE CASE REPORTS

Case 1 (Marked Improvement).—H. J. H., male, aged 46. Postencephalitic Parkinson's disease. The patient had severe influenza and probably encephalitis lethargica at the time of the 1918 to 1919 influenza epidemic. The present disorder had endured for over 10 years. The patient, a public accountant, was unable to conduct his work properly because of pronounced rigidity, excessive tremor of both upper limbs, difficulty in walking and inability to arise from the seated position. He had taken Rabellon, all of the existent belladonna preparations, also Neostigmine, Amphetamine and Tolserol, without much result. The patient presented the aspect of an advanced form of postencephalitic Parkinson's disease, with a propulsive, hemiplegic, parkinsonian gait. He sat in a chair with the body kept well forward and was unable to get up unless assisted. He could not start the gait, but had to be pushed gently forward. In attempting to turn his legs would catch, and he could not turn around unless assisted by having his legs unlocked. When starting to walk he thrust forward rapidly, with a hurried gait. On December 8, 1948 Benadryl therapy was started, with a dosage of 50 mg. four times a day, and hyoscine hydrobromide, 0.6 mg. four times a day. Benadryl hydrochloride was administered 35 mg. intravenously twice weekly. Within one week the patient noticed improvement in his gait, decided improvement in speech, and he was able to write, clothe himself and use his right hand, which he formerly was incapable of doing. There was distinct improvement in gait, rigidity, tremor, capacity to perform fine movements, state of well-being and appetite, and there was a gain in weight. These improvements were not only subjective, but they could be readily observed objectively by the patient's wife and by the examiner.

Case 2 (Fair Improvement).—C. E., male, aged 43. Postencephalitic Parkinson's disease of 23 years' duration. On admission to the hospital December 2, 1942, the patient showed the usual characteristics of postencephalitic Parkinson's disease, with marked festination, paresis of the right arm, immobile facies, marked rigidity of the left side of the body, tremor involving the left and right hand, inaudible speech and oculogyric crises almost daily. He had been receiving belladonna derivatives of all types and also Neostigmine for some period of time to no avail. On August 11, 1948 Benadryl therapy was started, with 50 mg. four times daily. The patient also received one tablet of Rabellon three times daily. In addition he was given Benadryl hydrochloride, 35 mg. intramuscularly, every other day. There was an immediate response and the patient straightened up, his gait improved perceptibly, speech became audible, and the oculogyric crises diminished and at times were not present for several days at a time. It was found that when the patient was having an oculogyric crisis, the injection of Benadryl hydrochloride, 35 or 40 mg., lessened the intensity of the seizure. He experienced a remarkable degree of well-being, and seemed to take a new lease on life. The appetite improved, and he gained 10½ pounds within the first two months of treatment.

Case 3 (Unimproved).—A. L. K., male, aged 47. Advanced postencephalitic Parkinson's disease of five years' duration. The present disorder began in 1944, at which time the patient noted a peculiarity in gait. At the end of that year it became markedly

abnormal, and he observed tremor of the left hand, then developed a left hemiplegic gait. He was studied in several clinics where the diagnosis of postencephalitic Parkinson's disease was made. The condition progressed very rapidly until he became completely bedridden. He had received all types of treatment prescribed for this disorder without benefit. The patient appeared very much older than his stated age of 47, and lay in bed completely immobile, with expressionless facies and marked rigidity. He was unable to move his head from side to side and had difficulty in rotating the eyes. The patient was quite depressed about his condition and the fact that his wife had to conduct his business and support the family. On January 15, 1949 he was placed on Benadryl therapy, 50 mg. four times a day, with hyoscine hydrobromide, 0.4 to 0.8 mg. four times daily, and Benadryl hydrochloride, 35 mg. intravenously twice weekly. In addition, he received a polyvitamin preparation intravenously twice weekly, and 2 ml. of whole crude liver extract every other day. During a three week period he showed absolutely no improvement with this form of therapy. He was then given Tolserol, alone and in conjunction with Benadryl and hyoscine, but this also proved of no value.

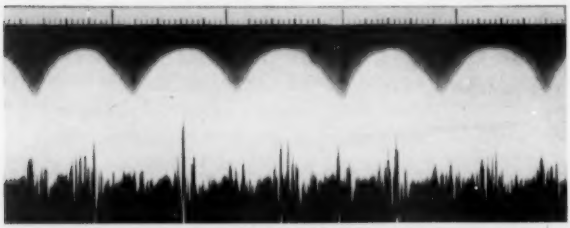

FIG. 1.—Electromyogram before medication—(electrode in gastrocnemius). Upper band 6 per second muscular contraction of tremors. Lower band records electrical potentials. (Courtesy of Charles F. Dieterle, M.D.)

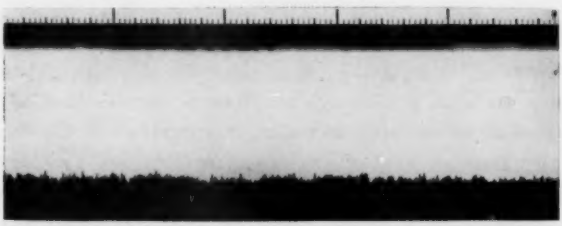

FIG. 2.—Tracing following Benadryl, 40 mg., intravenously. Observe cessation of tremor. Similar tracing obtained after injection of 0.6 mg. hyoscine hydrobromide. (Courtesy of Charles F. Dieterle, M.D.)

COMMENT

Several observers have noted that Benadryl antagonizes the spasm of smooth muscles.[6] Winder, Kaiser, Anderson and Glassco[7] showed that Benadryl, in addition to its histaminolytic action, had an atropine-like action and that it was capable of preventing in vitro spasms of guinea pig ileal strips elicited with barium chloride, acetylcholine or histamine.

Two of the patients in this series had electromyographic studies done following the intravenous injection of 40 mg. of Benadryl hydrochloride, and following the intravenous injection of 0.6 mg. of hyoscine hydrobromide. With both drugs mechanical and electromyographic tracings indicated cessation of tremor (figures 1 and 2). However, with Benadryl hydrochloride the effect came on much more rapidly and was more enduring.

It will be noted that among the 35 patients only three were of the arteriosclerotic type, whereas all eight patients reported by Budnitz[1] were classified in this group. The three arteriosclerotic patients in this study did not respond well enough to be included in the improved classification, whereas Budnitz' patients all showed improvement. The arteriosclerotic form of Parkinson's disease is a relatively infrequent one, the most commonly encountered form being the postencephalitic and idiopathic varieties. More recently Ryan and Wood[8] have reported the use of Benadryl in the treatment of 40 cases of parkinsonism and their results parallel those reported in this series.

SUMMARY

Thirty-five patients suffering from various forms of Parkinson's disease were treated with Benadryl. It was administered orally and parenterally, alone and in conjunction with belladonna drugs. The patients in this series did not fare well on oral Benadryl administered alone. The most striking and beneficial results were obtained when the drug was used together with members of the atropine group. Eighty per cent of patients in this series showed improvement, and 20 per cent were unimproved. None of the patients was made worse. Notable improvement was seen in the state of well-being, heightened morale, ease of performance of the various movements necessary in carrying out the day's work and activities, improvement of speech and ambulation. Tremor was much improved in early cases, but in moderate or advanced cases tremor was influenced relatively little except when the drug was given intravenously or intramuscularly. No alterations were observed in the hematologic findings after continued therapy. The only side effect was that of drowsiness which occurred in about 25 per cent of the patients, but that was overcome readily by the use of Amphetamine.

The results obtained in this study from the combined use of Benadryl and belladonna derivatives are superior to those which have been observed in the past using solanaceous drugs alone. This has been sustained throughout the course of treatment, but time alone will disclose whether

this form of antiparkinsonian therapy will ultimately share the fate of its predecessors.

ADDENDUM

Since the presentation of this paper, 17 additional cases or a total of 52 patients have been studied. The results obtained with the combined use of Benadryl and hyoscine have been consistently maintained as reported here. Artane (trihexyphenidyl), whose effects in parkinsonism were reported by Doshay and Constable,[9] has been used alone and in combination with Benadryl and hyoscine hydrobromide in 40 patients of this series. In the main the results with Artane conformed closely with those reported by Schwab and Tillmann.[10] Artane was found to be effective when used alone in approximately 15 per cent of cases. In about two thirds of those patients in whom the use of Benadryl and hyoscine hydrobromide proved insufficiently beneficial, the addition of Artane yielded superior results. The remaining one third of this group were not helped by the addition of Artane. Toxic reactions were observed in approximately 8 per cent.[11, 12]

Each patient with Parkinson's disease requires experimentation with the drugs employed in this series, used as single agents and in various combinations before the most satisfactory formula is achieved. From this it is evident that great flexibility must be exercised in the selection of drugs to be used in the treatment of this condition, and if failure results with the use of one or more of the antihistaminics or spasmolytics, then various combinations should be tried before admitting defeat.

The parenteral Benadryl hydrochloride used in this study was supplied through the courtesy of Doctor F. H. Nelden, of Parke, Davis and Company.

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• *Varieties of nerves.*—The nerves which connect a limb with the centres fulfill the following functions: They convey outwardly motor impressions, resulting in voluntary or involuntary motion, as the case may be. They carry centripetally the myriads of impressions which constitute sensations, or which, unfelt as sensations, are excitomotory in purpose. Lastly, a system of nerves, known as sympathetic, exercises control over the flow of blood to the tissues. Section of these nerves paralytically dilates the vessels; galvanization contracts them. This system originates in the spinal cord, but there is also evidence that certain spinal nerves, unrelated to the sympathetic, possess the power to cause directly enlargement of arterioles and increase of vasal supply.

—S. Weir Mitchell in *Injuries of Nerves and their Consequences*, published in 1872.

Neurologic Aspects of Fatigue

Robert S. Schwab, M.D. and John S. Prichard, M.D.

THE FATIGUE curve of a muscle-nerve preparation working against resistance and stimulated artificially is a familiar phenomenon. If the muscle is in good condition with adequate circulation, contractions at a rate of four to five per second may be maintained indefinitely. If the contraction rate goes up to five or six per second after a period of three or four minutes, the amplitude begins to fall off in a regular manner, and unless the stimulus current is increased in two or three minutes, the response disappears. A period of time must elapse before the muscle responds again to the stimulus. In the mammalian muscle this has been determined to be several minutes.

In clinical practice the fatigue curves in voluntary muscle in humans have been studied, and again this is a familiar phenomenon. The length of time necessary to produce the voluntary fatigue curve is much shorter than that of the muscle-nerve preparation. The number of contractions per second and the amount of resistance or weight involved determine the length and shape of the fatigue curve. When no more work occurs voluntarily, it has been supposed that the fatigue state of the muscle has been reached. However, this is not so, because in numerous adequately controlled observations reported in the literature and repeatedly confirmed by us, it has been possible by electrical stimulation to cause the muscle to contract promptly at the point when voluntary fatigue is complete. If the quadriceps muscle, for example, is used, a vigorous patellar reflex can be elicited at the point when voluntary power is gone.

The explanation of this phenomenon is not difficult to find, since there must be protective mechanisms in the living creature which prevent the occurrence of complete muscle fatigue described in relation to the muscle-nerve preparation. It is obvious that an animal who fatigues his heart or his diaphragm to the point of complete muscle exhaustion would imme-

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This work was supported by a grant from the Office of Naval Research, Project VIII.
Read at the first interim meeting of the American Academy of Neurology, Cincinnati, Ohio, April 15, 1950.

diately die before recovery could occur. It is necessary to block, therefore, the onset of fatigue in the muscle before it occurs by a feed-back mechanism of some sort.

This feed-back mechanism is composed of a delicate balance of the inflowing sensory impulses during a muscle contraction, adding to the metabolic effects contraction by-products (lactic acid and carbon dioxide) which produce in the living brain a condition or state that prevents the voluntary contraction from being initiated. Involved in this cessation of activity is an increasing desire to stop the action on a conscious level. This equilibrium is subject, of course, to many modifications and motivations, and a strong desire to complete the action will increase the period before the voluntary fatigue sets in.

There are essentially four sites of the development of fatigue seen in neurologic practice. The first one is in the muscle itself. In the diseased muscle with defective circulation, an inadequate number of fibers, or fibers that have been damaged by disease, the equilibrium mentioned in the previous part of the paper occurs much earlier. Such curves have been obtained in patients with progressive muscular dystrophy.

The second site of the disturbance produces earlier fatigue in voluntary contraction and is in the myoneural junction. This location is associated with the disease myasthenia gravis and many fatigue studies in this condition have been done. Neostigmine injected into the subject alters this abnormal condition at the myoneural junction, and a nearly normal ergogram is obtained. After removal of the thymus gland in a certain number of patients, this improvement is also achieved.

The third site of the involvement of fatigue is in the peripheral nerve or in the spinal cord. Fatigue curves have been studied in polyneuritis, neuritis, disseminated sclerosis, etc.

In the fourth group the fatigue is produced by the presence of excessive numbers of sensory impulses entering the nervous system beyond and above the normal ones from the muscle. This might occur in a patient with a painful joint around which the muscle is operating. The pain from the joint augments the normal sensory impulses from the muscle and produces a premature level of fatigue. A similar process takes place in Parkinson's disease, in which patients show marked fatigue curves; the explanation here is that the extrapyramidal system produces an increase in the sensory impulses, producing the fatigue state. A third and most complex example occurs in patients of the neurosis group and those with fatigue complaints that are produced by outside situations in their environment, since in such persons all impulses produce an early fatigue. We have made a detailed study of such cases in the past five years. It is

known that many patients with anxiety and tension states who are preoccupied with emotional problems of one sort or another have a complaint of fatigue. This usually disappears with successful psychotherapy and, of course, is not affected by the ordinary rest. It can be induced in normal subjects by artificial stresses, and when artificial stresses are added to an already existent psychoneurosis even greater fatigue occurs.

In the differential study of the complaint of fatigue it is not difficult to place the fatigue syndrome into the proper category in a very short time. Normal subjects report experiences of fatigue in relation to physical exercise. The fatigue is usually proportional to the amount of exercise, subsides promptly with rest, and is concerned with the muscles chiefly involved in this exercise. However, nearly all normal persons remember periods when they were excessively tired and complained of fatigue which was associated with emotional stresses of one sort or another, the removal of which promptly relieved the fatigue.

Patients who have myasthenia gravis complain excessively of fatigue from ordinary activities such as stair-climbing, chewing food, swallowing, talking, keeping the eyes open, holding up the head, etc. Their symptoms usually disappear with short periods of rest and tend to become exaggerated in the afternoon or evening. They disappear promptly with Neostigmine. Patients who have physical disease such as arthritis, neuritis and polyneuritis complain of fatigue in the use of specific muscle groups which previously were not fatigued by ordinary exercise. For example, a patient with poliomyelitis involving the left leg complains of fatigue in this limb with ordinary walking or stair-climbing, but he does not complain of fatigue in the arms, neck or the uninvolved leg.

In patients with neuroses the complaint of fatigue is generalized, vague and diffuse. It is often associated with other psychiatric symptoms and the words "lack of drive," "lack of ambition," "irritation," and "boredom" are commonly used. Their fatigue is usually worse in the morning after a night's sleep, and becomes less bothersome during the day.

Further differential tests consist in the use of Neostigmine and testing the performance of specific muscles, with the following results:

1. In normal persons there is a slight drop in the efficiency of the work done after an injection of Neostigmine.

2. In patients with myasthenia gravis, on the other hand, there is a dramatic and conspicuous increase in efficiency with the drug.

3. In patients with physical disease there is usually no change with Neostigmine, or perhaps an increase in the fatigue.

4. In patients with psychoneuroses there is usually a decrease in work output to a greater degree than in the other two states.

Electroencephalographic Evidence of Thalamic and Hypothalamic Epilepsy

Erna L. Gibbs and Frederic A. Gibbs, M.D.

IN THE COURSE of studies on the electroencephalogram in sleep, a new type of spike discharge has been encountered. It consists of two components, either of which may appear alone: 1) 14 per second positive spikes which have the general appearance of the typical 14 per second spindle of light sleep except that the spindle created by the 14 per second positive spikes is flat-topped (i.e., the negative phase is cut off); and 2) a component which consists of four to six per second positive spikes (figure 1). The 14 per second positive spike component appears at a level of light sleep when 14 per second spindles are common, and the six per second positive spike component appears in slightly deeper sleep. Although 14 and six per second positive spikes are not always associated, they are so closely related that in this first study it seemed wise to consider them together. They usually appear bilaterally, but are independent in each hemisphere. They are rarely restricted to one lobe; although diffuse throughout one hemisphere, they are usually of highest voltage in the occipital area.

A search was made for 14 and six per second positive spikes in the electroencephalograms recorded during sleep of 300 control subjects. This pattern was found in eight cases. In a group of 5,000 epileptics or suspected epileptics (table 1), 14 and six per second positive spikes were encountered in 312 cases, or six per cent. For the most part, the group of patients with one or both of these patterns had waking electroencephalograms which were essentially normal (table 2). Only 0.3 per cent of the group had any type of seizure discharge while awake, and during sleep only two per cent had abnormal discharges of types other than 14 and six per second positive spikes. It appears, therefore, that these positive spikes are abnormal; they are rare in normal control subjects and are three times as common in patients with epilepsy. They can be considered a distinct electroencephalographic entity because they do not

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The cost of this study was covered in part by a grant from the Rockefeller Foundation.

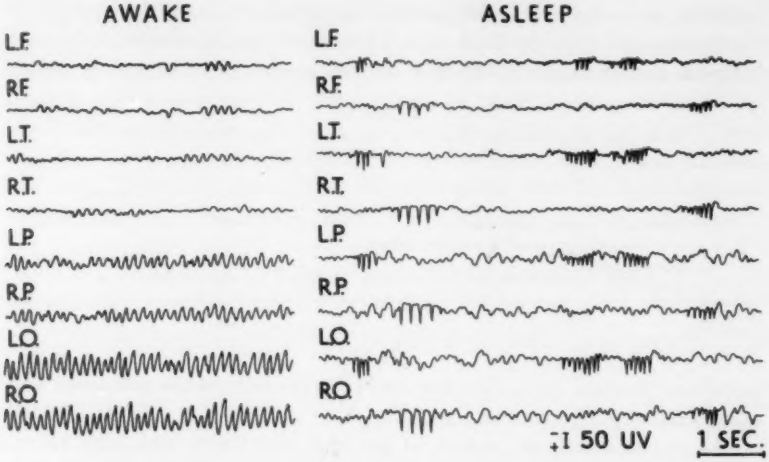

FIGURE 1. Sample strip from the electroencephalogram of a patient with "atypical epileptic seizures."
Recordings in the waking state are normal, but during sleep 14 and six per second positive spikes are evident in both hemispheres; they appear independently in each hemisphere. The tracings shown here were made with monopolar leads, the reference consisted of interconnected electrodes on the lobes of both ears. Abbreviations are as follows: L.—left; R.—right; F.—frontal; T.—temporal; P.—parietal; O.—occipital. Time (1 sec.) and voltage (50 microvolts) calibrations are shown in the lower segment.

correlate highly with other types of seizure discharge nor with other electroencephalographic abnormality.

Three hundred cases were selected which had as their only type of abnormality 14 and six per second positive spikes, either alone or in combination. All cases were carefully analyzed to determine their electroencephalographic and clinical characteristics. These patients were for the most part adolescent or young adults (table 3). This is believed to be due not to a selection artifact but to a greater susceptibility of young

TABLE 1
OCCURRENCE OF FOURTEEN AND SIX PER SECOND POSITIVE SPIKES AMONG EPILEPTICS AND CONTROL SUBJECTS

Number	*Diagnosis*	*No. with 14 and 6*	*Per cent*
5000	Epilepsy	312	6
300	Normal	8	2

persons to this type of disorder. Persons with seizure discharges of other types from the same general population have an entirely different age distribution; young children predominate in the group with petit mal

patterns, and adults 30 to 40 years of age predominate in the group with a psychomotor type of discharge. There were no significant differences between the incidence of 14 and six per second positive spikes among

TABLE 2
ELECTROENCEPHALOGRAPHIC FINDINGS ASSOCIATED WITH FOURTEEN AND SIX PER SECOND POSITIVE SPIKES

	Cases	*Per cent*
Normal or slightly abnormal (except for 14 and 6 positive spikes)	300	96
Seizure activity	8	3
Very slow	4	1
	312	100

males and females. In the present series, 54 per cent of the 300 cases were male, and 46 per cent were females.

As will be seen from table 4, 91 per cent of patients with both 14 and six per second positive spikes had these patterns bilaterally, but the discharge was always independent in the left and in the right hemisphere. In only three per cent of cases with 14 and six per second positive spikes was the discharge restricted to the left hemisphere; in six per cent it was restricted to the right hemisphere. So there appears to be no special tendency for this pattern to select the dominant hemisphere. Three per cent of the entire group had 14 and six per second positive spikes while awake. In cases with 14 per second positive spikes only (i.e., unassociated with six per second positive spikes), the discharge was unilateral in seven per cent and bilateral in 93 per cent. When six per second positive spikes were unassociated with 14 per second positive spikes, the discharge was

TABLE 3
AGE DISTRIBUTION OF PATIENTS WITH FOURTEEN AND SIX PER SECOND POSITIVE SPIKES

	Per cent
0-9 years	12
10-19 years	38
20-29 years	28
30-39 years	12
40-49 years	7
50 and over	3
	100

unilateral in 30 per cent and bilateral in 70 per cent. Thus, it is obvious that 14 per second positive spike activity is more commonly bilateral than six per second positive spike activity.

The general clinical complexion of the group is indicated by the diagnosis which these patients received prior to electroencephalographic study (table 5). A detailed analysis of the symptoms of this group is shown in table 6, and a summary of this analysis in table 7. Some patients had several types of seizure, and for the purpose of the present study, each was considered separate and distinct; i.e., the listing of seizures was non-exclusive. Thirty-six per cent of the total group had fainting spells and 49 per cent had convulsions. There was no history of convulsions in 35

TABLE 4
LATERALIZATION OF FOURTEEN AND SIX PER SECOND POSITIVE SPIKES

	Left		*Right*		*Bilateral*	
	No.	*%*	*No.*	*%*	*No.*	*%*
14 and 6 per second positive spikes	7	3	12	6	182	91
6 per second positive spikes only	14	17	10	13	57	70
14 per second positive spikes only	0	0	3	7	15	93

per cent of the total group. However, 65 per cent had a history suggestive of clinical epilepsy. Eighty-seven per cent had ictal symptoms, such as fainting attacks, crying spells, rage attacks, et cetera, which although not clinically diagnosed as epileptic could be called "epileptoid." Ten cases, or three per cent, had no ictal symptoms but complained of continual dizziness, weakness and headaches, apparently on the basis of previous head trauma. Transient paralysis and weakness occurred in four per cent of the cases, and in one case the symptoms were ipsolateral to the seizure discharge. (Such ipsolaterality was encountered also in two cases with unilateral seizures.) Attacks of pain outside the head are a rare complaint

TABLE 5
PRELIMINARY DIAGNOSIS OF PATIENTS WITH FOURTEEN AND SIX PER SECOND POSITIVE SPIKES

Diagnosis	*No. Cases*		*Per cent*	
Epilepsy				
Grand mal	137	196	46	65
Atypical	43		14	
Psychomotor	7		2	
Focal	5		2	
Jacksonian	4		1	
Petit mal	0		0	
Syncope	31		10	
Neurosis	15		5	
Post-traumatic syndrome	16		5	
Postencephalitic syndrome	11		4	
Psychopathy	9		3	
Hysteria	10		4	
Behavior disorder	7		2	
Psychosis	5		2	
Total	300		100	

TABLE 6

SYMPTOMS OF PATIENTS WITH FOURTEEN AND SIX PER SECOND POSITIVE SPIKES

Symptom	*No. Cases*	*Per cent*
Generalized convulsions	137	46
Syncopal attacks (including dizzy spells)	107	36
Attacks of pain (in head, arms, legs, trunk)	59	20
Attacks of numbness and paresthesia	57	19
Attacks of rage	56	19
(murder committed during)	4	1
Antisocial and vicious behavior	28	9
Attacks of nausea and vomiting	26	9
Vasomotor attacks (blanching, flushing)	23	8
Sleep attacks	18	6
Mental deficiency	12	4
Crying spells	11	4
Attacks of visual disturbance (hallucinations and blindness)	10	3
Attacks of fear	9	3
Attacks of dyspnea	8	3
Attacks of shivering	8	3
Cataplexy	7	2
Psychomotor seizures	7	2
Focal seizures (no march)	5	2
Auditory hallucination (music)	5	2
Attacks of gagging and choking	5	2
Attacks of tachycardia	5	2
Attacks of enuresis	5	2
Atypical Jacksonian seizures (alternating left and right sided march)	3	1
Sudden urge to micturate	3	1
Attacks of fever	3	1
Laughing spells	3	1
Attacks of headbanging	3	1
Oculogyric crises	3	1

in epilepsy, but in this series, attacks of severe pain in the arm, leg, or trunk occurred in seven per cent of the patients.

Detailed consideration of the types of epileptic seizure manifested by these patients is of interest. Forty-six per cent had generalized tonic-clonic convulsions, two per cent had psychomotor seizures and two per cent had focal seizures. One per cent had alternating focal seizures; i.e., at one time confined to the left side of the body and at another time confined to the right side of the body. One patient had true Jacksonian epilepsy with a sensory march from the arm. The complete absence of classical petit mal seizures is noteworthy, as is also the low incidence of psychomotor seizures. The most common aura for a seizure was pain. This occurred in 12 per cent of the patients. Usually this consisted of a sharp pain in the head. A pain in the stomach was next in point of commonness, but the chest, abdomen or other parts of the body are also sites of warning pains. Other specific types of aura were less common than pain, but if all patients with viscero-motor and vasomotor (i.e., vegetative) auras are grouped together, they are as numerous as those in which pain constituted the chief presenting

TABLE 7

SYMPTOMATOLOGY ASSOCIATED WITH FOURTEEN AND SIX PER SECOND POSITIVE SPIKES

Symptoms	*No. Cases*	*Per cent*
Convulsions	146	49
Disorders of body sensation (paresthesias and pain)	116	39
Syncopal attacks	107	36
Ictal vegetative symptoms (cardiovascular, respiratory, gastrointestinal and urinary)	90	30
Ictal disorders of emotion and emotional expression (including cataplexy)	84	28
Attacks of sleep	18	6

symptoms. A gastric aura, which is in general the commonest type of epileptic aura, occurred in only one per cent of the present group of patients, and no one had an olfactory type of aura.

Sixty-three per cent of the entire group had ictal symptoms which were not diagnosed as epilepsy. They were characterized as dizzy spells, fainting attacks and attacks of unconsciousness. In this group, loss of consciousness was often exceedingly prolonged, extending two or three hours.

TABLE 8

PRESUMPTIVE ETIOLOGY OF THREE HUNDRED CASES WITH FOURTEEN AND SIX PER SECOND POSITIVE SPIKES

Etiology	*No. Cases*	*Per cent*
Trauma	61	20
Encephalitis	21	7
Birth injury	9	3
Vascular accident	3	1
Carbon monoxide poisoning	2	1
	96	32
Near relative with epilepsy	20	7

A search for a common etiological factor was unrewarding (table 8). Although trauma seemed to be the most usual etiology, severe trauma was reported in only 10 per cent of cases.

DISCUSSION

Pain as part of an epileptic seizure in a mixed group of epileptics is rare, but as will be seen from table 6, it is common in persons with 14 and six per second positive spike discharges. The pain is usually intense and more nearly resembles the type of pain which occurs in trigeminal neuralgia than that which occurs in migraine. It flares up quickly and disappears relatively rapidly. Visceromotor and vegetative symptoms may

be thought of as a common type of aura in epilepsy, but such specific symptoms as pounding of the heart, gagging, etc., are rare in the general group of epileptics, though common in the present series. The high incidence of atypical seizures in this group and the high proportion of attacks consisting of vegetative and thalamic symptoms distinguish this group of patients from the general group of epileptics.

When convulsions occurred in the present series, they were commonly preceded by auras suggesting a thalamic or hypothalamic onset. It is no more surprising that convulsions appear as an accompaniment of thalamic and hypothalamic epileptic disorder than that convulsions appear as an accompaniment of a sensory Jacksonian seizure.

Even if there were no clinical evidence implicating the thalamus or hypothalamus in these cases, certain lines of experimental evidence would do so. Morison and his collaborators[1, 2] have shown that, in the cat, spindles which closely resemble the 14 per second spindles of sleep in man originate in the thalamus. More recent work by Magoun and Lindsley[3] has indicated that spindle activity is controlled from thalamic and hypothalamic areas. The diffuse but lateralized distribution of the 14 and six per second positive spikes suggests that they are mediated by nonspecific thalamic efferent systems.

The fact that 14 and six per second positive spikes have a positive electrical sign in all cortical areas, suggests that they originate subcortically. When recordings are made from a distant, relatively inactive reference electrode to the center of a discharging area, the spike seizure discharges are negative to the reference electrode. If the active electrode leads from an area which is beyond (in advance of) the discharging system, the spikes are positive.[4, 5]

Fourteen and six per second positive spikes differ from other types of spike discharge because they are not temporally associated with a clinical seizure. During the clinical seizures from which these patients suffer, the electroencephalogram is usually normal, or if seizure discharges appear, they are of the grand mal type (i.e., repeated diphasic or negative spikes). However, in one case where six per second positive spikes occurred during the waking state, the patient gagged or coughed simultaneously with each spike discharge. It is assumed that in the waking state, thalamic discharges reach the cortex only when and if they have attained a sufficient intensity to produce grand mal discharges in the cortex. It is assumed that during sleep, however, thalamic and hypothalamic centers are normally the pacemakers of cortical activity, and that disordered functioning in these deep centers appears as a distortion of the normal sleep patterns projected to the cortex (specifically the 14 and six per

second rhythms). That the disorder in these centers takes the form of spike activity, suggests an epileptic type of disorder; i.e., a failure to regulate the rate at which energy is released. Fourteen and six per second positive spikes are not, strictly speaking, a seizure discharge because they are rarely immediately associated with clinical seizures, but they correlate with epileptic types of clinical disorder, and we believe they can be properly considered as evidence of a deep-lying epileptic focus. Therefore, they are classified as epileptic patterns.

From what has been said about the symptomatology associated with 14 and six per second positive spikes, one might assume that such cases could be easily confused with psychomotor epilepsy. The assaultiveness of a patient with 14 and six per second positive spikes is usually precisely directed and skillfully executed. Four of the present series of 300 patients committed murder during a rage attack. This is a much higher incidence of murder than is encountered among patients with a psychomotor type of discharge. (In our own series of several thousand patients with psychomotor epilepsy, there have been no cases of murder.) During a psychomotor seizure, the patient is usually too confused and poorly coordinated in his movements to do much harm. Obviously, however, a patient may commit murder during a psychomotor seizure, and we have heard of at least two such cases, but the assaultive behavior of the psychomotor epileptic is like that of a "fighting drunk," and he is usually fairly easy to manage. Although behavior disorders are common in both groups, the interseizure behavior of the psychomotor epileptic is often bizarre and is referred to by the family as queer. The patient with 14 and six per second positive spikes, on the other hand, usually has a normal personality and his family complains chiefly of his episodes of meanness and cruelty.

Eight per cent of the total group of patients with 14 and six per second positive spikes were aware that their seizures were precipitated by emotional stress. This is a higher incidence of emotional precipitation of seizures than is found in any other group of epileptics. The etiology in the present series was so diverse that it seems reasonable to assume that the abnormalities in question can be produced by any of the factors which produce other types of epileptic disorder, for example, trauma, encephalitis, anoxia, and vascular disease.

The titer of 14 and six per second activity in any group will depend on how the group is selected. Although this pattern occurred in only six per cent of patients referred to an epilepsy clinic, it is to be expected that the incidence of such disorder will be higher in a group of patients with such diagnoses as organic neurosis, vasovagal attacks, pseudoepilepsy and hysteria.

SUMMARY AND CONCLUSIONS

Fourteen and six per second positive spikes have been encountered during sleep in six per cent of patients with a clinical history of epileptiform disorder, and two per cent of 300 control subjects. Such spikes are distorted forms of the normal sleep patterns which have been shown in animals to originate in the thalamus and hypothalamus. The diffuseness of the discharge and the general positivity of the spikes suggest a subcortical origin.

The clinical correlates of 14 and six per second positive spike discharges suggest epileptic disorder in the thalamus and hypothalamus; attacks of pain, rage, and vegetative symptoms are common. Though easily confused with psychomotor epilepsy and other epileptic syndromes, general and specific differences usually permit the informed physician to make a correct clinical diagnosis even without an electroencephalogram, but a record of the electrical activity of the cortex in sleep clinches the diagnosis. As compared with other types of epileptic and epileptiform disorder, 14 and six per second positive spikes are relatively benign. A few discharges of this pattern, particularly in children, in the absence of symptoms should not be regarded too seriously. They are likely to remain asymptomatic and disappear with increasing age. When symptoms are present, demonstration of such disorder is important not only as an aid to diagnosis, but as a clue to treatment. Fortunately, such disorder usually responds well to a combination of Dilantin and phenobarbital, or Dilantin and Mesantoin.

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• In connection with nerve wounds and their consequences, we have to deal with alterations due to the destruction or irritation of the various fibres of nerves which minister to pain, touch, the thermal sense, motion, calorification, and nutrition.

—S. Weir Mitchell in *Injuries of Nerves and their Consequences*, published in 1872.

Clinical Evaluation of ACTH and Cortisone In Myasthenia Gravis

Clark H. Millikan, M.D. and Lee M. Eaton, M.D.

THE CAUSE of myasthenia gravis remains obscure. It is known that acetylcholine is present at the myoneural junction when a stimulus passes from the nerve into the muscle, and there may be defective synthesis of this substance when myasthenia gravis is present. Neostigmine temporarily improves this defect, but the cause of the faulty formation of acetylcholine and the method in which Neostigmine works are not completely understood. In the search for further information about these mechanisms, Torda and Wolff[1] have reported that patients who have received adrenocorticotropic hormone (ACTH) have had, in all instances, striking improvement.

In an effort to define further the nature of the faulty metabolism present in myasthenia gravis and to test the effectiveness of the hormones in this condition, five patients consented to take ACTH or cortisone. Because of the fact that the course of myasthenia gravis is often characterized by sudden and extreme exacerbations and remissions, the five patients were chosen with great care. There was a history of long-term myasthenia without remission in every instance, and in two of them the disease was gradually becoming more severe. In such a group of myasthenic patients, a definite improvement in symptoms and physical signs following administration of the hormone would most likely be a result of the medication rather than of a spontaneous remission.

All of the patients studied underwent routine examinations in a general medical section and in the section on neurology and psychiatry at the Mayo Clinic. Tests of strength recorded in the case histories were done in the early morning before the first dose of Neostigmine was administered. It is known that more accurate comparative evaluations of strength can be made in this way than if the testing is done at variable intervals after Neostigmine has been ingested.

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Read at the first interim meeting of the American Academy of Neurology, Cincinnati, Ohio, April 14, 1950.

REPORT OF CASES

Case 1.—A man aged 23 years was first seen at the clinic on May 24, 1943, at which time he complained of generalized weakness. He related that in March 1940 he first had noticed muscular weakness around the hips and legs, especially after walking a few blocks. By 1941 this weakness included the arms, and by 1942 the eyelids and tongue were also weak. He became steadily worse until six months before his admission to the clinic. He had been unable to raise his arms above his head or to comb his hair, and his voice had become nasal and his speech slurred, particularly late in the day. A month before examination it was necessary for him to use crutches for the first time.

Physical examination revealed the following positive signs: bilateral ptosis, impaired lateral ocular rotations, a 2 to 3+ weakness (on the basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition) of the facial, palatal and pharyngeal muscles, and 3 to 4+ weakness of the muscles of the shoulder girdle and pelvic girdle..

A clinical diagnosis of myasthenia gravis was made. The result of the Neostigmine test for myasthenia was positive, and the patient ultimately left the clinic with instructions to take six 15 mg. tablets of Neostigmine bromide per day, and three capsules containing $\frac{3}{8}$ grain (0.024 gm.) of ephedrine sulfate per day. During the time he received this medication the patient showed marked improvement and was able to walk without crutches and get up and down steps with almost normal strength.

The patient was seen at the clinic again in 1944, at which time his condition was essentially unchanged. He was taking six to eight tablets of Neostigmine bromide and three capsules of ephedrine sulfate per day. He was able to work as an apprentice optician.

On November 30, 1949 the patient again entered the clinic. There had been no change in the medication, and he related that his symptoms were slightly worse than at the time of his previous visit.

On December 8 administration of ACTH was started. A solution of ACTH was injected intramuscularly three times a day, with a total daily dose of 100 mg. of ACTH. Injections were continued for eight days. During the last two days of administration the patient was worse and became so weak that he was unable to rise from a sitting position without aid from another person.

On December 17, the day following cessation of ACTH administration, it was noted that he was unable to raise his arms into the air at all and he still could not get out of a chair without assistance. By December 23 the patient was able to get out of a chair without assistance and could get his arms partially into the air, although with great difficulty. This was the same muscle strength he had had before administration of ACTH. On December 27 it was noted that there had been no essential change in the patient's physical condition, although he stated that subjectively he was somewhat improved.

Early in February 1950 a second course of eight intramuscular injections, each daily dose totalling 100 mg. of ACTH, was given. On the sixth day of injection there was increased weakness of all the involved muscles. Shortly after completion of the course of injections this added weakness disappeared. Again, there was no alteration in the abnormal physical signs or in the amount of Neostigmine taken daily by the patient as compared to the abnormal physical signs present or the amount of Neostigmine taken before the use of ACTH.

The third series of daily intramuscular injections, each daily dose totaling 100 mg. of ACTH, was begun on March 16, 1950. Fifteen hundred milligrams of ACTH was given, an increased amount being injected because of the lack of change in the condition of the patient after he had received smaller quantities of ACTH. There was progressive increase in the weakness during the last week of this series of injections, so that the patient had great difficulty in eating and walking. Two days after the last of this series of injections improvement of muscle strength began and has continued. The strength at the time when this paper was written was equal to that which was recorded before the administration of the ACTH.

Case 2.—A woman aged 36 years was first seen at the clinic on October 1, 1948, at which time she complained of difficulty in swallowing, talking and breathing. She had been well until February 1948, at which time she noticed drooping of the right eyelid, even in the morning, which became worse as the day progressed. By March 1 there was also some impairment of speech. During the third week in March the patient entered a hospital elsewhere for a three week stay, and was given dicumerol for multiple sclerosis. All of her symptoms improved during the period of observation, at which time she was resting in bed. Early in April, double vision was noted for the first time. Administration of Neostigmine bromide was started. The dose varied from two to five tablets per day. By August 1948 there was severe weakness in both upper extremities and the dose of Neostigmine was gradually increased until the patient was taking 8 tablets per day.

Physical examination revealed the following positive signs: almost complete bilateral ptosis, variable impairment of ocular rotation, slurred speech, weakness of all the facial muscles, weakness of the bite, weakness through both upper extremities, more severe on the left than on the right, and weakness of intercosal and diaphragmatic function. A diagnosis of myasthenia gravis was made. Symptoms were regulated best when approximately 10 to 12 tablets of Neostigmine bromide were taken per day. The patient was dimissed from the clinic.

Letters from the patient and from her physician related that her symptoms gradually grew more severe, until it was necessary for her to have 18 to 30 tablets of Neostigmine bromide a day to be able to be up an about. She returned to the clinic November 5, 1949, and related that during the preceding year she had gradually become worse and was having more difficulty with shortness of breath, swallowing, weakness of the neck muscles and generalized weakness. She was taking between 65 and 75 tablets of Neostigmine bromide per day.

Physical examination revealed the following positive signs: severe bilateral ptosis, impairment of all ocular rotations, slurred nasal speech, severe weakness of the facial muscles, of the bite and of swallowing, severe weakness of the neck and of both upper extremities. A roentgenogram of the chest showed a lobulated anterior mediastinal tumor at the level of the hilus, predominantly on the left side. Roentgenoscopic examination confirmed this finding. The basal metabolic rate was +4 per cent.

Between November 5 and November 14, 1949, it became apparent that the patient's symptoms were gradually growing more severe. Four to six tablets of Neostigmine bromide, administered 45 minutes before the evening meal, would not make it possible for her to eat. The entire matter was discussed with the patient and with her husband and, in view of the fact that her condition would not permit operative removal of the thymic tumor, it was decided that she should receive cortisone.

While at complete rest in bed the patient was able to get along on 18 to 30 tablets

containing 15 mg. of Neostigmine bromide per day. In addition, she received a total of 1 to 5 mg. of Neostigmine methylsulfate per day by injection as seemed necessary. Between November 15 and November 29, the patient received a total of 1,500 mg. of a suspension containing cortisone intramuscularly in doses of 100 mg. every day. Between December 3 and December 10, she received 1,500 mg. of a solution containing cortison intramuscularly in doses of 100 mg. the first day and, thereafter, 200 mg. per day.

Because of severe difficulty in swallowing and difficulty with respiration, tracheotomy was done on December 13 and the patient was placed in a respirator. The results of examination of the spinal fluid on December 19 were entirely negative. Dihydrostreptomycin and penicillin were given in an attempt to control infection in the trachea, lungs and bladder, but the patient regressed steadily and she died on December 21, 1949.

Case 3.—A woman aged 36 years was first seen at the clinic on June 18, 1946, at which time she complained of generalized weakness. She related that in 1941 there had been an onset of weakness of the right hand, drooping eyelids and difficulty in controlling the movements of the muscles of the eyes so that there had been diplopia. Later in 1941 came difficulty in swallowing and regurgitation of fluids into the nasopharynx. Following the onset of these symptoms, there was improvement until February 1944 when all of them became more severe and the administration of Neostigmine was advised by a physician. Four or five tablets of Neostigmine bromide gave considerable relief, and the patient's condition remained essentially unchanged.

Physical examination revealed the following positive signs: 1+ bilateral ptosis, slurred nasal speech, weakness of all the facial muscles and some weakness of the jaw-muscles. A clinical diagnosis of myasthenia gravis was made. The dose of Neostigmine was increased to 8 tablets per day, and control of the myasthenia gravis was satisfactory. The patient was also given a capsule containing $\frac{3}{8}$ grain (about 0.024 gm.) of ephedrine, three times a day.

The patient was not seen again until May 12, 1947, at which time she related that her symptoms had become steadily worse. She was taking 10 to 12 tablets of Neostigmine per day, and the use of ephedrine seemed to give no benefit. Positive signs on physical examination were much the same as at the time of the preceding visit to the clinic, but the weakness was more severe in each instance.

On November 3, 1948, she was admitted to the hospital for a trial of the effect of cortisone. In order that the clinicians observing the patient might make unbiased statements concerning their observations, administration of cortisone or of a control substance, cholesterol, was continued from December 4, 1948, until January 12, 1949. All the material administered was similar in appearance, but a certain amount of it, known only to one person, contained cortisone while the remainder was chemically inert. On December 24, it was noted that the patient's symptoms had become much more severe and that the findings on physical examination had changed to definitely worse. It became very difficult for her to swallow. There were increased weakness of all the face and neck muscles and great difficulty in chewing and swallowing, and respiration became labored. The clinicians requested from the committee some knowledge concerning the contents of the drug being given to the patient. It was found that she had received 100 mg. of cortisone each day for the preceding six days. At the request of the clinicians, the committee discontinued the use of cortisone at that time, but the patient continued receiving the injections of cholesterol.

On January 12, 1949, it was again noted that the patient's condition had become

alarmingly worse, so much so that it was considered too dangerous to continue administration of the drug, and knowledge was again requested from the committee as to the contents of the material injected. It was found that the patient had received cortisone for the preceding seven days in doses of 100 mg. per day. At that time, administration of the drug was discontinued. The patient was taking from 10 to 15 tablets of Neostigmine bromide per day.

The patient left the hospital, but subsequent reports in late January, early and late February and early March, 1949 revealed that she improved so that her strength was equal to that before she was treated with the drug. She continued taking 8 to 14 tablets of Neostigmine bromide per day.

The clinic was informed on April 11, 1949 that the patient had died suddenly on April 8, 1949.

Case 4.—A woman aged 23 years was first brought to the clinic on March 9, 1949. She stated that she had been well until September 1945, when after a bicycle hike, she noted a rather sudden onset of severe fatigue and weakness in the back and both legs. Continuation of routine activities for the next week produced constant fatigue and then there was gradual improvement. In January 1947 diplopia, drooping of the eyelids and dysphagia began. These features continued, and during the winter of 1948-1949 there was more and more difficulty with the legs, back and arms, so that the patient could walk only a few feet and would frequently drop objects from the hands.

In January 1948 thyroidectomy was performed, following which there was very slight improvement of the dysphagia, diplopia, ptosis and general weakness. The patient was still unable to walk, and her speech was indistinct because of weakness. In August 1948 a diagnosis of multiple sclerosis was made, and the patient was given tetra-ethyl-ammonium chloride. On one occasion, after she had been given this medicine, there was severe respiratory depression, and she became cyanotic and required artificial respiration and oxygen therapy. For the three months of 1949 preceding her admission to the clinic, her course had been stationary. She was barely able to eat, to talk or to lift her head from the bed. She was unable to walk, and there was extreme weakness of the upper extremities, lower extremities and back.

Physical examination revealed the following positive signs: 3+ ptosis bilaterally, 1+ impairment of ocular rotations in all directions, severe weakness of the facial muscles, 2 to 3+ weakness of all muscular structures in the shoulder girdles and upper extremities and in the pelvic girdles and the lower extremities with depression of all stretch reflexes. Th patient was unable to walk. The results of the general examination and further neurologic examination were essentially negative.

Following the hypodermic injection of a solution containing 1.5 mg. of Neostigmine methylsulfate, the patient was able to walk, smile, close her eyes, whistle and lift her head from the bed, and had fairly good strength in the upper extremities. The diagnosis of myasthenia gravis was made.

On March 16, 1949, the patient's course had been regulated so that she was taking six to eight tablets of Neostigmine bromide and three capsules of ephedrine sulfate a day. She could walk without support for the first time in two years, and had much better use of her general musculature, although her performance was not normal. She was not able to work. On August 3, 1949, the patient returned to the clinic. Her symptoms and the abnormal physical signs had not changed, and she stated that she was taking five to seven tablets of Neostigmine bromide every day.

Beginning on August 15 the patient received 100 mg. of ACTH every day for 12

days. The solution containing the ACTH was injected three times a day. There was marked increase of weakness during the last portion of this period. The patient was unable to sit up without support or to lift a glass of water to her mouth.

Three days after the final injection improvement began, and by November 11 she was able to walk well but was still unable to walk on her heels or toes. She needed to take four tablets of Neostigmine bromide and three capsules of ephedrine sulfate to have almost normal strength.

By December 3, the muscle strength had decreased almost to the value present before the patient received ACTH. She again received 1,200 mg. of ACTH, the final injection being given on December 14, 1949. Strength decreased toward the end of this course and then began to increase two days after its completion. By January 17, 1950, improvement was so great that the patient used only one tablet of Neostigmine bromide a day, and examination revealed that all of the affected muscles had returned to almost normal strength. On March 9, 1950, it was noted that strength was decreasing but was still better than at any previous examination at the clinic. The patient was taking five tablets of Neostigmine bromide every day and had voluntarily increased the dose as her strength had decreased.

Case 5.—A man aged 40 years was first seen at the clinic in 1933, at which time he complained of blurring of vision which had been present off and on since 1918, double vision since 1931, drooping of the right eyelid since 1932, weakness of the right leg since late 1932, drooping of the left eyelid since February 1933, trouble in speaking clearly and difficulty in swallowing since March 1933.

The results of physical examination were essentially negative except for 2+ bilateral ptosis, impairment of all ocular rotations of both eyes, inability to close the eyes completely, inability to whistle and a nasal type of speech.

A diagnosis of myasthenia gravis was made, and the patient was instructed to take 30 gm. of glycine every day.

The patient was not examined again until January, 1940. He had progressed fairly well with mild exacerbations and remissions. In December 1939 there was a marked change in the patient's voice and more difficulty in swallowing. Physical examination revealed paralysis of the left vocal cord, in addition to the phenomena noted in 1933. Routine laboratory examination of the urine and blood showed normal values, but roentgenograms of the chest showed the shadow of a mass in the upper left part of the mediastinum. The patient received roentgen therapy to this mass without any benefit to the impairment of speech or difficulty in swallowing.

In 1945 the patient complained that all of his symptoms were worse and that he was having more trouble in swallowing, more trouble with drooping of the eyelids and more difficulty in walking. Physical examination again revealed bilateral ptosis with difficulty in completely closing the eyelids and wrinkling the forehead, marked impairment of ocular rotation and weakness of both iliopsoas groups of muscles. There was marked improvement of strength following the oral administration of 15 mg. of Neostigmine bromide. Roentgenograms of the chest were reported as showing a small tumor mass anterior to the left hilus, approximately the same size as it was in 1940. The symptoms were much improved when the patient took five or six tablets of Neostigmine bromide per day. A week after beginning this medication, tablets of ephedrine sulfate were given three times a day, in addition to the Neostigmine bromide.

The patient was seen again on June 3, 1946, at which time he reported that he was working normally and taking eight tablets of Neostigmine bromide and three

capsules of ephedrine sulfate per day. The patient was advised to have thymectomy performed, and he returned home to consider this advice.

On July 26 thymectomy was performed and 28 gm. of tissue was removed. This contained a nodule of residual thymoma 1.5 cm. in diameter, the remainder being thymic fat. The postoperative course was uneventful and on August 7, 1946, it was noted that the patient was doing well while taking three tablets of Neostigmine bromide and three capsules of ephedrine sulfate per day. The patient was not working.

December 30, 1947, the patient was seen for examination and stated that he had been able to work full time while taking three to four tablets of Neostigmine bromide and two capsules of ephedrine sulfate per day. However, two weeks preceding the visit, he had noted greater difficulty in talking and eating and for the first time in almost a year had been having diplopia. The dose of Neostigmine bromide was increased to eight tablets every day and the patient was much improved.

On August 4, 1948, the patient reported that he was taking 14 tablets of NU1317 (synthetic physostigmine-like substance) every day and that he felt better than he had for more than a year. He also was taking two capsules of ephedrine sulfate per day.

In October 1949 the patient was examined again. He stated that he was again taking Neostigmine bromide because it seemed to give him more effective relief than any other drug. He was able to continue working if he took eight to 12 tablets of Neostigmine bromide and three capsules of ephedrine sulfate every day. Physical examination revealed the following positive signs: moderate ptosis bilaterally, thick speech, inability to whistle, marked weakness of the shoulder girdle and pelvic girdle, ability to squat and rise only one time and 2 to 3+ weakness of the neck. When he attempted to lie down, he fell back. He was unable to lift his head off the pillow.

After discussion with the patient it was decided that he should receive a course of cortisone acetate. Between November 1 and November 19 he received a total of 1,500 mg. of a suspension of cortisone acetate injected intramuscularly. Each dose contained 100 mg. of the drug. After ten injections of the drug there was decrease of the patient's strength so that he was unable to squat and rise, unable to swallow and unable to lift his arms into the air. At this time he was taking 10 tablets of Neostigmine bromide a day. By November 28, 1949, his strength had increased so that muscle power was equal to that present before the administration of cortisone. By January 17, 1950, the patient had been able to reduce the dose of Neostigmine bromide to two or three tablets every day, and examination revealed that muscle strength was moderately improved when compared with that present before administration of cortisone.

COMMENT

It should be emphasized that great care was used in the selection of these patients. While it cannot be said that a uniformly favorable response in all of the patients would have been absolute proof of the beneficial action of ACTH or cortisone, such a response would have been definite evidence in favor of such an interpretation. However, complete failure of improvement in two of the patients is evidence that ACTH or cortisone is not the ultimate answer to the problem of myasthenia gravis. The two patients who had the greatest degree of improvement have gradually become worse. Certainly, whatever beneficial effect is present appears to be a transitory one.

Because of the increase in symptoms during the last part of a course of ACTH or cortisone, caution must be used when administering these substances to myasthenic patients. Patients with great weakness may become worse to the point of decompensation of respiratory function and to the point where Neostigmine will not provide an adequate margin of safety.

SUMMARY

Five patients suffering from myasthenia gravis consented to receive one or more courses of injections of cortisone or ACTH. In every patient increased muscle weakness was observed toward the end of every course of cortisone or ACTH. Two patients had no improvement, one patient had slight transitory improvement, one patient had moderate transitory improvement and one patient had marked transitory improvement after completion of the courses of cortisone or ACTH.

Until time elapses for further study of the three surviving patients the evidence is that cortisone and ACTH are of limited value in the treatment of myasthenia gravis.

REFERENCES

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• In the normal condition, the sense of pain is very unequally distributed as regards the skin surfaces, and bears no definite proportion to the acuteness of the tact sense. Indeed, there are certain portions of the tissues in which it is extremely deficient, as the back and a limited space over the tibia. As a rule, the thigh is less sensitive than the arm, the leg than the forearm; but as no complete study of this sense has been made, it is impossible to carry such comparisons further. In the lower animals the dorsal skin seems, in some cases, to possess little or no feeling, so that I have actually made incisions through this part in dogs and rabbits without seeming to produce any pain whatsoever. The interior organs are variably provided, as to the pain sense, some of them appearing to have little or none of this form of sensibility; yet in all, even in the bones and intestines, lie remote capacities for torture which seem capable of development in the presence of diseased states.

—S. Weir Mitchell in *Injuries of Nerves and Their Consequences*, published in 1872.

Treatment Review

Medical Therapy of Epilepsy

Francis M. Forster, M.D.

Prior to the year 1857 there was no effective medical therapy for epilepsy. In that year, quite by accident, Sir Charles Locock introduced the use of bromides. The rationale for the use of bromides in epilepsy was the anti-aphrodisiac effect, and it was noted incidentally that the frequency of seizures was also decreased. No great innovation in medical therapy of epilepsy was made until 1912 when Hauptmann[1] introduced the use of phenobarbital. The next major achievement in therapy occurred in 1938 when Merritt and Putnam[2] introduced sodium diphenylhydantoinate (Dilantin). This new drug marked the beginning of an era in concluding and deducing rational therapy. Merritt and Putnam felt that, although bromides and phenobarbital were both anticonvulsants and sedatives, it need not be necessary for an anticonvulsant to be a sedative. For this reason, they began a search of potential sedatives and screened for anticonvulsant effect those potential sedatives which had not proved effective in producing sleep. The most effective anticonvulsant of this group was found to be Dilantin sodium. Subsequent important advances in the therapy of epilepsy include the introduction by Lennox[3] of oxazolidines in the handling of petit mal epilepsy, and the further investigations into the hydantoin groups.[4]

This rapid increment in knowledge regarding therapy of epilepsy is paralleled by the rapid advance of clinical, surgical and laboratory understanding of epilepsy. Neurologists of the present era are in a good position to assay properly the nature and cause of seizures and to determine the proper mode of therapy. However, we still have before us unexplored areas of therapy and laboratory procedure which serve as incentives to further study.

The essential problems in medical

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treatment of epilepsy are the following: (1) When is epilepsy severe enough to be treated? (2) When is medical therapy indicated? (3) What medical agents do we have available, and what are their particular pharmacologic characteristics? (4) What are the indications for certain drugs?

INDICATIONS FOR TREATMENT

Virtually all patients who have seizures should be treated for these seizures. The only exception is the patient who has had a single major convulsion and in whom there is no evidence of a specific disease which requires therapy. It is generally not advisable to treat a patient for a single seizure. Under certain circumstances, however, it may be quite essential that the person who has had a single seizure be treated. This is determined to some degree by the occupation and station of the patient. A pregnant woman who has had a single seizure should, of course, be treated in order to prevent further seizures during the course of pregnancy. Likewise, a fondling mother who has had a single seizure should be treated with as much regard for the child as for the mother. Patients in professions or in life work where a seizure would be especially deleterious, despite a history of a single seizure, likewise should undergo therapy.

INDICATIONS FOR MEDICAL THERAPY

Certain patients with seizures must be treated surgically. In these instances treatment is directed to the cause of the seizures and not to the seizures themselves. The patient with a brain tumor or subdural hematoma must necessarily undergo surgery, and the treatment is intended to correct the underlying disease rather than merely eliminate seizures. Patients with idiopathic or genetic epilepsy cannot be treated surgically at the present time. By genetic or idiopathic epilepsy, we mean those patients who have petit mal or generalized seizures with a generalized seizure discharge in their electroencephalogram, who present a positive family history of seizures, whose neurologic examination is negative, and whose history and laboratory study are negative for a focal brain disease or general systemic disease which could cause the seizures. Certain patients with symptomatic epilepsy should also be treated medically. All patients whose seizures arise from cerebral scars or other diseases for which physical therapy is not mandatory are entitled to at least a preliminary course of medical therapy. There are certain exceptions to this, for example, the patients with focal seizures or generalized seizures followed by postictal paralysis which becomes more marked after seizures, or patients who, following seizures, show a mental defect increased by each seizure.[5] Therefore, it may be said that all patients with idiopathic or essential epilepsy and many patients with symptomatic epilepsy should receive medical therapy. In the group of symptomatic epilepsy cases, there is still one further line of treatment if medical therapy proves unsuccessful. Under the proper conditions, recourse may be had to surgery.

MEDICATIONS FOR CONTROL OF SEIZURES

The most important anticonvulsant medications at the present time come under three classifications: the barbiturates, the hydantoinates, the oxazolidines. Of the barbiturate series, the drug having the greatest anti-

convulsant element is phenobarbital. It is available in tablets of 0.015, 0.03 and 0.1 grams, and in some parts of the country 0.065 gram tablets are available. The minimum effective dose for an adult is 0.05 grams, and the maximum dose that can be tolerated is seldom greater than 0.4 grams. Phenobarbital is one of the oldest and safest of the anticonvulsants, its only toxic symptom being drowsiness in the larger dosages. The other barbiturates are considerably less effective than phenobarbital. This is a point well worth emphasizing since in status epilepticus, the real emergency in epilepsy, many general practitioners, internists and others employ Nembutal, Amytal, Seconal or others of the barbiturate series with less potency than phenobarbital. Of course, phenobarbital cannot be administered parentally, but the sodium salt is readily available for intravenous or intramuscular injections.

Sodium diphenylhydantoinate (Dilantin) is the oldest of the hydantoids and is available in 0.1 gram capsules. The minimum effective dose for an adult is 0.3 grams per day, and the maximum dose that can be safely administered is 0.7 grams per day. Minor complications produced by sodium diphenylhydantoinate are hypertrichosis and hyperplasia of the gums. Neither of these is as serious as some would indicate and the hyperplasia of the gums is not associated with a vitamin C deficiency. Hypertrichosis, of course, can be controlled by dipilatories or shaving. The hyperplasia of the gums is often controlled partially by massage. If this fails and the hyperplasia is very marked, oral surgery may be employed for deletion of the hypertrophied gums. This is practical especially when the sodium diphenylhydantoin has proved the most effective anticonvulsant drug for the particular patient. More serious complications of Dilantin therapy are drowsiness, particularly with the larger doses, ataxia, nystagmus and occasionally diplopia. Flatulence and nausea sometimes occur during Dilantin therapy. This is often remedied easily by altering the time of medication in relation to meals.

The next hydantoinate in chronological sequence is Mesantoin or methyl phenylethylhydantoin. This is available in scored tablets, each containing 0.1 grams of the active ingredient. The minimum effective dose is 0.3 grams per day, and up to 1.0 grams and 1.2 grams may be tolerated. Originally, Mesantoin was introduced as a more efficacious hydantoinate than Dilantin, and also a less toxic one. It is true that hypertrichosis, hyperplasia and ataxia seen in Dilantin sodium treatment are less evident in patients treated with Mesantoin. However, Mesantoin has become known as a dangerous anticonvulsant, since severe aplastic anemias[6] and fatal hepatitis may occur in the course of Mesantoin therapy. This drug must, therefore, be considered in the class of dangerous anticonvulsants and careful watch must be made for the development of untoward signs. Its chief usefulness is in cases refractory to other medications. Undoubtedly there are certain patients with seizures which can be controlled at the present time only by Mesantoin.

Recently, Thiantoin has been introduced. This is available in white capsules containing 0.12 grams, and red capsules containing 0.23 grams of the active ingredient. This is apparently a safer anticonvulsant than Mesantoin and is less apt to produce toxic results, but, in general, is not as efficacious as sodium diphenylhydantoin or Mesantoin. There have been a few

unreported instances of severe hepatitis occurring during the Thiantoin therapy.[7, 8]

Of the oxazolidines, two derivatives are available. These are Tridione and Paradione. Tridione is available in large white capsules with a distinct cocoanut flavor, which contain 0.3 grams of the active ingredient. Paradione is available in red round perles, each containing 0.3 grams of the active ingredient. The minimal effective dose is 0.3 grams per day, and the maximum dose is 2.7 grams per day. The complications of these medications are meralopia and blood dyscrasias.[9] Meralopia is the blurring of vision when suddenly entering into bright light. This is not a serious complication and readily remits after the cessation of oxazolidine therapy. The blood dyscrasias are both agranulocytosis and aplastic anemias. Both meralopia and blood dyscrasias are more common during Tridione therapy than during Paradione therapy, although Paradione cannot be considered entirely safe. Other medications which have been tried without a high incidence of success include d-l-glutamic acid, atropine and amphetamine sulphate. The latter is of use chiefly in combatting drowsiness or sluggishness in patients receiving large doses of barbiturates or hydantoinates.

Experimental medications not yet available on the open market but showing some promise include phenylacetylurea (Phenurone), Nuvarone, Hibicon and Geminal. The first of these, Phenurone, is an open chain compound but still is closely allied to the other three groups of anticonvulsants. This product is manufactured in 0.5 gram scored tablets. The first successes were reported by Gibbs in 1947.[10] Dosage is 1.5 to 3.5 grams per day. Complications and toxic symptoms[8] include psychiatric disturbances, gastrointestinal disturbances, headache, insensitivity to pain,[11] hepatitis and aplastic anemia.[12] Obviously, these complications are serious. Most important are the psychiatric complications which occur in approximately 20 per cent of patients receiving the drug. The psychiatric disturbances are usually severe depression, and there have been occasional suicides. It is interesting to note[13] that psychiatric manifestations develop most frequently, if not exclusively, in patients with temporal lobe foci in their electroencephalograms. Nuvarone is a new and experimental hydantoin, and is not yet available on the market. It shows promise of being efficacious, particularly along the same lines as the other hydantoinates. Geminal is a phenobarbital-like medication, and is still in the experimental stages. Hibicon also is still in the experimental stage, and it is not certain whether it shows sufficient promise to be released.

INDICATIONS FOR PARTICULAR DRUGS

The preceding paragraphs have covered the standard, and to some extent, the experimental medications available for control of seizures. Obviously, when so many medications have been developed, no one has yet proved to be completely successful. Therefore, there must be particular indications for particular medications. Some are of particular value in certain situations and contraindicated in others. Before outlining these indications and contraindications, it is necessary to describe briefly the various types of seizures. The most important factors in determining the type of medication to be used are the type and frequency of seizure.

Seizure types may be classed in

four categories. Major convulsions are of the typical *grand mal seizure* type without an aura of focal connotation. The mode of onset is generalized without a constant deviation of the head, eyes or body to one side, and the tonic and clonic components are equal on the two sides and involve all four extremities. After the seizure, there is no postictal deficit to suggest a primary area of cortex from which the seizure emanated. The next category of seizures are the *petit mal seizures*, and the third, the *psychomotor seizures*. The differentiation between these is not difficult.[14] In general, petit mal seizures occur in children and psychomotor seizures occur in the adult. Petit mal seizures occur with great frequency during the day, as many as 100 or 200 not being unusual, and it is seldom that the patient has a seizure free day. Psychomotor seizures occur with the usual frequency of major convulsions, one a week, two a week, one in three weeks, etc. Moreover, seizures which occur during the night and arouse the parents are very seldom petit mal; they are, if in the minor seizure category, psychomotor in type. The actual seizure duration is very short in petit mal, usually less than a minute, while psychomotor seizures last from one minute to five or more minutes. Petit mal seizures are characterized[3] by short stares, a few mild chronic jerks or a sudden dropping to the floor and rising quickly, whereas in psychomotor seizures there is irrelevant but purposeful activity through which the patient is amnesic. Petit mal seizures cannot be finally diagnosed, however, unless the bilaterally synchronous three per second wave and spike formations are evident in the electroencephalogram.[15] The fourth category of seizures is *focal convulsions*, and this includes such attacks as Jacksonian motor, Jacksonian sensory, head-eye deviation seizures, auditory, visual-hallucinatory seizures, vertiginous seizures, etc.

From the standpoint of therapy, the major convulsions and focal seizures can be grouped together. That is, focal seizures which are not treated surgically and are to be treated on a medical regime are handled in general as though they were major convulsions. Medications most efficacious in major convulsions are phenobarbital and the hydantoinates. The oxazolidines are contraindicated in the treatment of major convulsions for they may increase the number of major convulsions. The only exception to this is the occasional patient with major convulsions preceded by petit mal attacks forming a sort of premonitory phase, and whose electroencephalogram shows a build up through three per second wave and spike discharges into the generalized convulsions. This relatively uncommon situation is better controlled with Tridione and phenobarbital. However, with this exception in mind, the medications of choice in major convulsions are phenobarbital and the hydantoinates. Patients with infrequent major convulsions who have not received adequate phenobarbital therapy should be tried on this medication first. Patients with frequent seizures, or those with infrequent seizures who have received fairly adequate phenobarbital trial, should be placed on Dilantin sodium. The minimal dose for adults is 0.3 grams. Dilantin should be considered the mainstay of therapy and should be continued until either the seizures are controlled or, if not controlled, the maximum or sub-toxic top minimal dose is reached. Once the top tolerated dosage or the maximum dose it attained and this fails to control seizures,

relatively small doses of phenobarbital may be employed nocturnally and spread through the day. If this routine fails, the Dilantin may be replaced in part by one of the other hydantoinates, either Thiantoin or Mesantoin.

Patients with petit mal seizures should be treated with phenobarbital and the oxazolidines. The hydantoinates are contraindicated in this group of patients, because petit mal seizures are precipitated or increased with their use. It is seldom that phenobarbital alone can control seizures in the patient with petit mal epilepsy. However, it is worthwhile at the patient's initial visit to introduce phenobarbital in small doses morning and night, and to order all the necessary laboratory studies. By the time the patient returns from the laboratory studies, it is evident almost invariably that phenobarbital will not control his seizures. Recourse must then be had to the oxazolidines. However, if phenobarbital is successful, this is all to the good. The choice between the two oxazolidines, Paradione or Tridione, is about equal. In general, Tridione is slightly more efficacious than Paradione, but also slightly more dangerous. Fortunately, however, patients whose seizures are not controlled by one of these may be well controlled by the other, so that the mere fact that one of them has failed does not preclude the successful use of the other. It is a wise practice to begin with one capsule in the morning, later increasing, if the seizures persist after four or five days, to one at morning and at noon. The dosage is gradually increased by one capsule per day until a total of nine is reached. If this does not obliterate seizures, the other oxazolidine may then be substituted for one dosage. For example, a patient begun on 0.3 grams of Tridione increased to 2.7 grams who still has attacks may then be placed on 2.4 grams of Tridione and 0.3 grams of Paradione, and after several days, 2.1 grams of Tridione and 0.6 of Paradione, etc. It may be discovered that at some intermediate point it is possible to stop the seizures with a combination of Tridione and Paradione. When the oxazolidines are instituted, phenobarbital should be maintained, for as noted previously the oxazolidines will occasionally precipitate major convulsions. The continuation of the phenobarbital therapy tends to offset this possibility. When phenobarbital and oxazolidine therapy has failed to relieve the seizures in petit mal epilepsy, the next line of treatment is far less efficacious, but it is at these times that atropine, caffeine, benzedrine or glutamic acid therapies can be instituted. While these offer little hope, there is an occasional patient who has benefited by one of these medications.

The treatment of psychomotor epilepsy is not entirely clear at the present time. A very conservative approach[16] to the problem of therapy is the energetic use of standard medications for major convulsions, namely phenobarbital and hydantoinates. On this regimen, from one third to two thirds of the patients with psychomotor seizures can have their attacks controlled. Those patients who still have seizures despite the use of phenobarbital and the hydantoinates can be treated with Phenurone. However, any patient with a severe or moderately severe personality problem should not receive Phenurone therapy. In any event, during the course of medical therapy all patients with psychomotor seizures should have frequently repeated electroencephalograms taken in the sleeping state.[17] The patient with psycho-

motor seizures is a potential candidate for neurosurgical procedure. If, during the course of medical therapy, electroencephalograms are taken at bimonthly or trimonthly intervals and in the sleeping state, the presence and delimitation of a temporal lobe focus may be much sharper at the time when surgery may become mandatory.

It has been noted above that the patient with major convulsions should not be treated with the oxazolidines, nor petit mal patients with the hydantoins. Obviously, there are a number of patients who have both major seizures and petit mal seizures, and it would seem that here both types of efficacious medications would be cancelled out. However, this is not quite as it seems. The patient who exhibits two types of seizures usually presents one of them as a major problem. For example, a child with 100 petit mal seizures per day, and only three grand mal seizures in his life, obviously has a major problem in the control of the petit mal seizures, and not the grand mal seizures. Conversely, the patient with weekly major convulsions, from whom a history of petit mal attacks is elicited only by direct questioning, has as his prime problem the control of the major convulsions. One should, therefore, proceed to deal with the major problem, explaining to the family, or the patient, the potentialities of augmentation of the other kind, or of at least no relief for the present. This is simply the development of the principle of first things first.

GENERAL CONSIDERATIONS

In the administration of medications, it is important to determine several factors with the patient. The first of these is the nature of the problem. In this modern day when every man considers himself a scientist, each patient is quite willing to accept the fact that his is an individual case, and that the solution will be found only by constructive research on the part of the physician with the patient's cooperation. Patients accept willingly the need for the trial and error method, when this is pointed out and when the judgment for choosing certain medications is explained to them. The need for careful and judicious taking of medication must be elaborated. Many patients do not understand that once a dosage is maintained which will render them seizure free, this dosage must be kept up until the physician determines it is not necessary to maintain full dosage. It is well to explain these factors at the very first session with the patient, and to set an arbitrary seizure-free time after which gradual reduction of medication can be attempted. For example, in a patient who has been having biweekly major seizures, it is determined at the first meeting that after a seizure-free period of two years, drugs can be reduced until the patient is both free from seizures and free from medication. This is the ultimate goal of treatment of all epileptic patients, namely freedom from seizures and freedom from medication.

Any patient taking medications other than phenobarbital or Dilantin sodium should have blood counts at least once a month, and these must be charted. Any serious decrease in white blood cells, in granulocytes or in red blood cells suggests that a blood dyscrasia may result if medication is continued. Development of jaundice in any patient on medication other than Dilantin sodium or phenobarbital is suggestive of a drug-induced hepatitis and likewise demands quick withdrawal of medication.

The most common pitfalls in the medical therapy of epilepsy are encountered in the inadequacy of dosages employed and in the abrupt transfer from one medication to another. The minimum effective dosages have been outlined previously. Perhaps the most abused drug in this regard is Dilantin sodium, for it is still common to find patients with a history of having been treated for eight or nine years with 0.1 to 0.2 grams per day. On the simple addition of sufficient Dilantin sodium they are rendered free of seizures. It is important to realize that the hydantoinates and phenobarbital differ radically in regard to speed of action and duration of action. Phenobarbital is a quick acting drug over a short period of time, whereas Dilantin sodium does not begin to take effect for some four or five days after the beginning of administration in adequate doses. Patients are sometimes confused by this, for they may forget to take their Dilantin sodium for a few days, then take the full complement of medication for that day, only to have a seizure that night, the time when the decrease in medication takes its effect. They then conclude that Dilantin sodium is of no avail in the control of seizures because they had no attacks while not taking it for several days, but had attacks while taking it. Occasionally, patients believe, or their doctors conclude, that they have developed a tolerance to hydantoinates because they suddenly develop a flurry of seizures after being carried seizure-free for a year or a year and a half. This sudden appearance of a flurry of seizures should not provoke the quick conclusion that the patient has developed a tolerance. Instead, the patient should be questioned specifically about the amount of medication missed four or five days prior. The proper way to ask this question is not, "Did you stop taking your medicine?", but, "Why did you stop?", and the usual answer is, "I thought I was cured." If the sudden flurry of seizures is not the result of a decrease in medication, the second most likely cause is intake of a fair amount of alcohol just prior to the reappearance of attacks.

Another pitfall in the usage of the hydantoinates is the method of transfer from phenobarbital to hydantoinates. This is not as prevalent now as it was some years ago. One occasionally sees a patient who has been on phenobarbital, and the physician suddenly decides to change from the phenobarbital to a hydantoinate. He makes a quick shift, cutting off the phenobarbital completely and introducing hydantoinates, with a disastrous flurry of seizures which are attributed to the administration of Dilantin, rather than to cessation of phenobarbital. The proper way to transfer from phenobarbital to hydantoinates is to administer full doses of both for three or four days, and then gradually decrease the phenobarbital over a period of four to eight days to the final level desired.

There are certain psychological factors in the handling of epileptics which are considered at this point. Every patient or parent of a patient has several questions in mind, such as: "Does this affect my mind?", "Will this make him a different kind of person?", "Will he ever be able to get married?" These questions are primarily questions of heredity, of deterioration, of epileptic personality. It is important to explain that, as far as the matter of deterioration is concerned, most patients and relatives who ask these questions have in mind an unfortunate individual who has had serious brain damage, and as a

result has had both seizures and deterioration. Deterioration is seldom caused by convulsive seizures[17] alone, and then only by frequently repeated major convulsions. It is important to remember that a common cause for apparent deterioration in epileptics is the injudicious use or over-dosage of medications with a sedative effect. Fortunately, this is a type of deterioration which is quickly remedied by decreasing medication, but in order to be properly appreciated, it must be properly diagnosed. In regard to the matter of epileptic personality, most authorities in the field of epilepsy at the present time believe that there is no such thing as a real epileptic personality. What one is assaying usually is a reaction of the patient to attitudes of the people in his environment, and the bitterness and narrowness of the so-called epileptic personality merely reflects the difficulties cast in his way by employers, prospective employers, prospective fiancees, fellow employees and family.

The question of marriage is essentially the question of children. It is a prime right of every individual to marry, and neither the physician nor the individual state has the moral right to interfere with any person's utilization of his God-given rights. The matter of children is another story, and each epileptic must at least make his spouse acquainted with the fact that he does have seizures. The factors which determine the possibility of epileptic off-spring are: the type of epilepsy in the parent, whether it is idiopathic or symptomatic; the personal and family history of seizures of the spouse and the epileptic parent.[18] In general, one out of 200 people has seizures, so that the over all expectancy is that one out of each 200 children born would have seizures. When one parent is an epileptic, the frequency rises to one out of 40; when epilepsy is symptomatic in one spouse, the other spouse having neither seizures nor family history of seizures and having a normal electroencephalogram, the possibilities are decreased to one out of 80 or one out of a 100. On the other hand, if the parent with seizures has an essential or genetic epilepsy, and the spouse has an abnormal electroencephalogram and a family history of seizures, the possibility of seizures rises still more than one out of 40.

It is important to convince the epileptic patient that he does not stand alone in the world. The very fact that one out of 200 people has seizures, and that there are 5,000 epileptics in a community of a million, is, in itself, a useful argument. Moreover, the feeling of belonging can be further augmented by membership in a group. The group which best serves this purpose is the American Epilepsy League, through which it is possible for the patient to obtain information regarding his disease presented at a layman's level, and he is also offered the feeling of group activity.

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• To attempt the consideration of all the means which have been employed in the treatment of epilepsy would be a hopeless task. Their mere mention would require several pages of this treatise. I shall therefore content myself with detailing the methods which I have found most useful.

First among remedies are the bromides of potassium, sodium, or lithium. The first should be given to adults in doses of at least fifteen grains three times a day, and is generally required in larger quantity. It acts very much better when largely diluted with water. A saturated solution contains about thirty grains to the drachm, and a half a teaspoonful or more should be mixed in at least a gill of water. Latterly I have used the bromide of sodium in doses a little smaller. It is, I think, more readily assimilated, and is less apt to produce gastric irritation, but, in other respects, its action is similar to that of the corresponding potassium salt. The bromide of lithium has a more immediate action; but I have not succeeded in obtaining any continuous effects from it in epilepsy which I could not derive from the potassium or sodium salt, and its great cost is a bar to the lengthened administration.

—William A. Hammond in *A Treatise of Diseases of the Nervous System*, published in 1871.

Neurology

Clinical Pathologic Conference

Case Record from the Department of Neurology, College of Physicians and Surgeons, Columbia University, and The Neurological Institute of New York

PRESENTATION OF CASE

The patient, a 65 year old white female, entered the hospital with the chief complaints of:

1) Impairment of memory for recent events for the past 6 to 8 months;

2) Intermittent generalized headaches for the past 6 months;

3) Left hemiparesis including the face for the past 3 months.

Past Medical History: Two and one half years prior to admission, the patient had suffered from myelogenous leukemia, manifested symptomatically by progressive weakness and easy fatiguability for several months. At that time she was treated with x-ray over the spleen and responded satisfactorily. About one year prior to admission a second course of x-ray therapy was given, again with good results. In addition the patient suffered from hypertensive vascular disease of several years standing.

Family history: One sister had a history of diabetes mellitus and hypertension.

Present illness: Following the second course of x-ray therapy for leukemia about one year prior to admission, the patient was well except for some impairment in memory until approximately six months before admission. At that time her daughter noted "attacks of stiffness," during which she had a staring expression for a few minutes but did not lose consciousness and was able to respond to commands. No convulsive movements were noted. These episodes occurred once or twice a week for a few months, but had not been noted for several months prior to admission. At approximately the same time it was noted that she became very agitated on occasions. She frequently clutched at her chest complaining that she was having a heart attack. Several physicians saw her during these attacks and concurred in a diagnosis of neurosis. It was noted at the same time that the patient's memory for recent events became poor and she was frequently confused. About three months prior to admission left-sided weakness was noted and two and one half months prior to admission to the Neurological Institute, she entered another hospital for study. At this time a markedly enlarged spleen was noted

Discussion by members of the neurological and neurosurgical staff.

H. Houston Merritt, M.D., presiding. Abner Wolf, M.D., neuropathologist.

but the peripheral blood was not markedly abnormal and it was felt that the leukemic process was relatively quiescent. An electroencephalogram was said to reveal a right-sided focus, and the daughter was informed that the patient had had a slight stroke. Following discharge from the other hospital she continued a downhill course and became a difficult problem for care at home because of her frequent attacks of confusion.

Physical examination: On admission the blood pressure was 170/95 mm. Hg., pulse rate 80 per minute, temperature 99° F. and respirations 20 per minute. The patient was obese, confused, appeared chronically ill but in no great distress. The heart was enlarged to the left; rate and rhythm were normal; and there were no significant movements. The lungs were clear to percussion and auscultation. The spleen was markedly enlarged, filling the left half of the abdomen to a point halfway between pubis and umbilicus. The liver was slightly enlarged. There were marked bilateral varicosities of the lower extremities.

Neurologic examination: The patient was right handed. She was able to walk only with support. No atrophy or fasciculation of muscles were seen. She showed a left hemiparesis with moderate weakness of the left upper extremity, somewhat less of the left lower. The reflexes in the left upper extremity were slightly more active than those in the right, but those in the lower extremities were equal. The abdominal reflexes were absent. No pathological reflexes were elicited. Testing for nonequilibratory coordination was not successful because of poor cooperation. Similarly, sensory examination was unsatisfactory. It was felt however that no gross changes were present. Examination of the cranial nerves revealed a supranuclear facial weakness on the left. The remainder of the cranial nerves showed normal findings; there were no changes in the fundi except for some vascular narrowing.

Laboratory data: Blood counts showed 13.6 Gm. of hemoglobin; 4.31 millions of red blood cells; 16,550 white blood cells with a differential count of 68 per cent polymorphonuclear cells, 10 per cent immature forms and 22 per cent lymphocytes; a few normoblasts were seen in the smear; platelets, 270,000; sedimentation rate, 2 mm in 1 hour; bleeding time, 1 minute; venous clotting time, 8 minutes; hematocrit, 48.8. NPN, 60 mg. per cent; sugar, 99 mg. per cent; CO_2 combining power 51; chlorides, 603; Mazzini, negative; urine, specific gravity 1.018, albumin 2+; stools, negative.

Lumbar puncture on admission showed an initial pressure of 320 mm. CSF. The fluid was clear and colorless. It contained 18 white blood cells (36 per cent polymorphonuclears) and 150 mg. of protein per 100 ml. Four days later lumbar puncture showed an initial pressure of 440 mm. CSF. The fluid was slightly yellow, contained 29 white blood cells (75 per cent lymphocytes) and 94 mg. per cent of protein. Final pressure was 55 mm. CSF. No leukemic cells were found in a centrifuged specimen. There was no untoward reaction to either lumbar puncture.

X-ray studies showed a normal chest and normal skull. A left abdominal mass, probably spleen, was revealed by flat plates of the abdomen.

Electroencephalogram showed a diffusely abnormal record with bilateral signs, but no clearcut focal or lateral signs.

Electrocardiogram was reported to be within normal limits.

Course in hospital: During the week of hospitalization the patient's course ran slowly downhill, although vital signs remained stable. At first the patient's episodes of confusion, disorientation and drowsiness apparently cleared up spontaneously. The NPN remained elevated with readings up to 60 mg. per cent on several occasions. On the second day of hospitalization the left pupil was found to be widely dilated with a sluggish response to light; on the following day the right pupil was slightly larger than the left. A therapeutic trial of local radiotherapy to the head was suggested by the medical consultant but the patient died before it could be started. Neurosurgical consultants felt that neurosurgical intervention was not indicated at the time. During the last

days the patient again became drowsy for long periods, responding poorly to commands or questioning, in spite of the usual supportive measures. On the seventh day of hospitalization she became progressively more comatose and unresponsive. Respirations rose to 40 and pulse to 135 per minute. The pupils were asymmetrical and unreactive to light. The patient became cyanotic and died.

DISCUSSION

DR. GILBERT GLASER: The clinical history of leukemia offers the obvious explanation that the picture was caused by leukemic infiltration of cortex and meninges.

DR. PAUL F. A. HOEFER: I agree, but would consider multiple hemorrhages more likely in a case of this nature.

DR. H. HOUSTON MERRITT: Infiltration of the brain substance is rare in leukemia, while meningeal infiltration is more common.

DR. BERNHARD DATTNER: I am impressed by the rapid fall of the spinal fluid pressure from 440 to 55 mm. and by the high protein content of the spinal fluid. The first electroencephalogram indicated a right-sided weakness. Therefore I feel we are most probably dealing with a rapidly expanding, space-occupying lesion.

DR. DANIEL SCIARRA: When this patient was on the ward a few months ago she presented quite a problem in the differential diagnosis between cerebral leukemia and infiltrating brain tumor. She was presented as such a problem at several of our conferences. At about that time Netzky and Adams each reported findings at the meeting of The American Neurologic Association, indicating that leukemic infiltration of the cerebral substance does occur. Prior to autopsy almost everyone on the staff felt this was a case of leukemic infiltration.

AUTOPSY REPORT

This woman suffered from three independent conditions. One of these was a severe generalized arteriosclerosis with relatively little involvement of the cerebral arteries and intense changes in the coronary vessels. In addition, she showed the pathological changes of a chronic myeloid leukemia with myelofibrosis consequent to x-ray therapy. Her intracranial expanding lesion was not part of the picture of the leukemia. Only rarely do mass lesions due to leukemic infiltration develop in the brain. More often one encounters hemorrhages and less frequently minor, multiple, often microscopic, leukemic infiltrations in the leptomeninges and parenchyma. The hemorrhagic lesions give rise to the sudden appearance of neurological manifestations, rather than the progressive, though rapid, course seen in this case. Her intracranial lesion was a large glioblastoma of the right temporal lobe and island of Reil which had extended through the splenium of the corpus callosum and cisterna ambiens into the left temporal and occipital lobes. For the most part, the neoplasm was well demarcated, variegated in color, soft to palpate and friable. Where it crossed the midline, it was white or greyish white and more homogenous and diffuse. Histologically, it was composed of a great many elongated bipolar cells and variable numbers of astrocytes and was highly vascular and extensively necrotic. The small blood vessels showed a good deal of hyperplasia of their walls. Many moderate-sized fresh hemorrhages were present in and about the neoplasm in each cerebral hemisphere. These were larger than the average commonly encountered in glioblastomas and may have been in-

tensified by the leukemia and perhaps by the hypertension from which the patient suffered. Herniation of the right cingulate gyrus was seen beneath the falx and of the right uncus into the incisura of the tentorium as a consequence of the supratentorial tumor, since the large mass was on the right. Histologically a small implant of glioblastoma into the leptomeninges was noted at the base of the medulla which must have originated from the tumor invasion of the subarachnoid space in the region of the cisterna ambiens.

SUMMARY

DR. MERRITT: This patient presented the unusual picture of two separate diseases. It was pointed out, however, that some of the findings indicated a space-occupying lesion.

DR. LAWRENCE POOL: In retrospect, I should like to point out that the heart attacks as well as the episodes of confusion shown by this patient might be the result of the temporal lobe lesion. Scoville has reported these two phenomena in response to electrical stimulation of the uncus.

• Having thus alluded to the external appearance of the brain we will now briefly notice some of the internal arrangements of this organ. On cutting into, or cutting off a portion of the brain, the first thing attracting attention is the difference of color between the external and internal parts of the brain. The outer part is of a grey color and of a soft and pulpy texture, and appears to encircle the inner, which is white and fibrous. The outer is called the grey, the cineritous, or the cortical part of the brain; the inner is called the medullary, or white. The cineritious part envelops all the convolutions, and by this arrangement—this folding up as it were, of the outer surface of the brain—its extent is greatly augmented beyond what it would be if the surface was uniform and smooth. This cineritious portion seems to receive a larger supply of blood than the white, and while the latter is very similar in appearance and structure to the nerves, the cineritious bears no resemblance to any other part of the system.

There are also some partial cavities called ventricles, within the brain. There is a large one in each hemisphere of the cerebrum. These are called the lateral ventricles, and are frequently found distended with fluid after death from disease of the brain. On dissecting the brain in various ways, parts have been seen which from some resemblance to other objects have received names accordingly. These appearances and the names given to them will be found in anatomical works, to which I refer the reader for more minute accounts of the structure of the brain.

—Amariah Brigham in *An Inquiry concerning the Diseases and Functions of the Brain, the Spinal Cord and the Nerves*, published in 1840.

Case Report

Herpes Zoster of the Right Trigeminal Nerve with Left Hemiplegia

William Newton Hughes, M.D.

Herpes zoster of the trigeminal nerves is frequently seen in neurologic practice, but it is rarely found associated with hemiplegia. The following is a case report of herpes zoster of the right trigeminal nerve with left hemiplegia.

PRESENTATION OF CASE

A woman aged 70 was admitted to the hospital on February 3, 1948, complaining of shingles of five weeks' duration and of weakness of the left arm, left leg and left face of one day's duration. The patient had been well until about January 1, 1948, when herpes zoster developed on the right side of the forehead and upper part of the face. Constant, moderately severe pain accompanied the herpes. A skin ointment and boric acid ointment for her right eye gave some relief. On January 27, 1948, one week before admission to the hospital, she developed a very severe pain "deep in the right side of her head" and different from the pain which she had had originally. On February 2, 1948, about 24 hours before hospital admission, she awoke and found her left arm, left leg and the lower part of her face extremely weak. She had difficulty in speaking because of weakness in her left lower face. She had severe pain in the right upper frontal region.

Physical examination showed the patient to be conscious, rational, alert and well oriented. There were erythematous scars from herpes zoster over the right forehead and face down to the corner of the mouth, extending exactly to the midline of the face. There was a left supranuclear facial paralysis with its accompanying speech difficulty. The tongue protruded in the midline. No stiffness of the neck was apparent. There was definite left hemiplegia with deep reflexes exaggerated on that side. There were bilateral Babinski reactions. Abdominal reflexes were not obtained, probably because of a fatty abdomen.

Urine analysis was normal except for 1 plus protein, 8 to 10 red blood cells, an occasional white blood cell and 6 to 8 coarse granular casts in the sediment. Blood studies were normal. Roentgenograms of the chest were negative except for a sclerotic arch in the aorta. Roentgenograms of the skull showed moderate hyperostosis of the inner table of the frontal bone; there were no destructive changes; the sella turcica was essentially normal; there were some calcifications in the central portion of the falx cerebri; pineal calcifications were in the midline; there was no evidence of increased pres-

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Read at the first biennial meeting of the American Academy of Neurology, French Lick, Indiana, June 1, 1949.

sure or signs of an expanding or calcified tumor; slight calcification was seen in the walls of the intracranial portions of the internal carotid arteries on both sides.

On February 4, 1948, 6 ml. of clear cerebrospinal fluid were removed by lumbar puncture. Initial pressure was 150 mm. of water and the final pressure was 110 mm. There were 4 erythrocytes and 51 lymphocytes per cu. mm. The total protein was 34 mg. per 100 ml., and the colloidal gold curve was 1111110000. On March 5, 1948, 7 ml. of clear cerebrospinal fluid were removed. There were 72 erythrocytes and 59 lymphocytes per cu. mm. and the total protein was 100 mg. per 100 ml.

Left hemiplegia became complete during the first few days of hospitalization and recovery was very slow in spite of intensive physiotherapy. On February 19, 1948, seventeen days after onset, slight motion was noted in the left biceps muscle. On March 8, 1948, slight adduction of the left arm was apparent. On March 19, 1948, a posterior plaster shell was applied to prevent further foot drop. At the time of discharge to a convalescent home on April 8, 1948, the patient was regaining motor power slowly and to a greater extent in the left arm than in the left leg. Since that time progress has continued slow, possibly due in part to insufficient nursing care and physiotherapy.

DISCUSSION

Cerebral thrombosis as a complication of herpes zoster might explain the hemiplegia and associated cerebrospinal fluid findings in this case. The onset of hemiplegia on awaking in the morning appears typical. In the writer's experience with cerebral thrombosis, the presence of 50 lymphocytes per cu. mm. in the cerebrospinal fluid and their persistence for over a month are most unusual. Ordinarily the cerebrospinal fluid protein does not become elevated several weeks after onset. However, cerebral thrombosis may still be the most likely explanation of the hemiplegia and associated spinal fluid changes.

Postinfectious herpes zoster encephalitis has been considered as the cause of the hemiplegia and cerebrospinal fluid changes. The increased lymphocyte count of the cerebrospinal fluid persisted for over a month as is often the case in similar types of encephalitis such as that associated with mumps. Merritt, Mettler and Putnam[1] state, "Cerebrospinal fluid abnormalities usually associated with this disease (herpes zoster) are mild pleocytosis (usually 5-50 white blood cells per cu. mm., chiefly lymphocytes), and increased protein (50-100 mg. per cent) in about one-half the patients. The spinal fluid changes may precede the cutaneous eruption." The cerebrospinal fluid protein in the present case was normal at onset, but increased to 100 mg. per 100 ml. later. This may occur in certain known virus infections such as poliomyelitis. There seems to be no reason why it could not occur also in herpes zoster.

The viruses of herpes simplex and herpes zoster are at times considered to have a very close relationship. Whitman, Wall and Warren[2] reported isolation of virus of herpes simplex from glycerolated brain material from two cases of fatal encephalitis with clinical features characterized by disorientation and drowsiness with the late appearance of minimal reflex changes. The clinical picture of the present patient, considered as possibly due to virus encephalitis from herpes zoster, is certainly quite different from the reported cases of herpes simplex encephalitis. Taterka and O'Sullivan[3] found all the motor complications of herpes zoster in 44 cases from the literature on the same side as the herpes. Nine-tenths of these motor complications were in the same segmental distribution as the

herpes. Herpes preceded paralysis in three-fourths of the cases and followed it in one-fourth of the cases. Paralysis developed from one day to two months after the herpes. Facial paralysis occurred with otic zoster, and oculomotor palsy occurred with ophthalmic zoster. In the upper extremity the deltoid was the chief muscle paralyzed, and in the lower extremity, the quadriceps. Paralysis did not occur in hemiplegic distribution as in the present case report. There were no spinal fluid findings reported, and so no information on cell count and protein was available for comparison.

Lemmon[4] reported a case of herpes zoster with weakness and pain in the right arm and shoulder, almost complete right deltoid paralysis, weak right trapezius, and atrophy of supraspinatus and of thenar eminence. The biceps, triceps and radial reflexes were absent. There was no leg involvement. Spinal fluid studies were negative. Attention is directed to this case, since it is fairly typical of the motor complications usually seen.

SUMMARY

Herpes zoster of the trigeminal nerves is frequently seen in neurologic practice, but is rarely found associated with hemiplegia. A case is reported with 50 lymphocytes per cu. mm. and with an increase in protein in the cerebrospinal fluid from 34 mgm. to 100 mg. per 100 ml. several weeks after the onset.

Taking the clinical picture as a whole, either cerebral thrombosis complicating herpes zoster or postinfectious herpes zoster encephalitis is considered as the most likely diagnosis for the hemiplegia and spinal fluid findings. The diagnosis of postinfectious herpes zoster encephalitis is seriously considered because similar spinal fluid findings are not encountered in cerebral thrombosis.

REFERENCES

1. Merritt, H. H.; Mettler, F. A., and Putnam, T. J.: Fundamentals of Clinical Neurology, Philadelphia, The Blakiston Co., 1947.
2. Whitman, L.; Wall, M. J., and Warren, J.: Herpes simplex encephalitis, J.A.M.A. 131:1408, 1946.
3. Taterka, J. H., and O'Sullivan, M. E.: The motor complications of herpes zoster, J.A.M.A. 122:737, 1943.
4. Lemmon, G. B., Jr.: Herpes zoster with motor involvement, U.S. Nav. M. Bull., 43: 357, 1944.

• Are we to suppose that there exist always in these organs pain nerves, and that only once, perhaps, in a lifetime these filaments are to be aroused in activity? Or, as regards the skin, how shall we deal with the like difficulty if we choose to believe that everywhere are peculiar nerve fibres devoted only to transmitting painful sensations? The skin, in this view of the case, must have a set of nerves so rarely used that it is difficult to comprehend how they can sustain their organic life uninjured, and ready to awaken into functional activity at long and irregular intervals.

—S. Weir Mitchell in *Injuries of Nerves and Their Consequences*, published in 1872.

Neurology

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF NEUROLOGY

DR. FREDERIC H. LEWEY

On October 5, 1950 at his summer home near Pennsburg, Pennsylvania, Dr. Frederic H. Lewey died of coronary thrombosis at the age of 65. A native of Berlin, Germany, and son of an eminent Berlin internist, he was descended from a family that included Dr. Paul Erlich among its members.

German neurology was at its peak when Dr. Lewey studied as an undergraduate and followed his post-graduate studies, and he was fortunate to obtain his neurologic education from the masters in the field. In his first clinical semester he studied neuroanatomy with von Monakow in Zürich. Later he obtained his training in neuropathology from Nissl, Alzheimer and Spielmeyer in Munich, and did neurophysiologic work with Magnus in Utrecht. His clinical education in neurology was under the direction of H. Oppenheim and R.

Cassirer and he took his psychiatric education under Kraepelin in Munich.

Two years after his graduation (Berlin 1910), Dr. Lewey became director of the laboratories of the Neuropsychiatric Clinic at the University of Breslau, which was one of the International Brain Institutes. He was there only two years until the outbreak of the First World War, during which Dr. Lewey served as a major in the German army, first in France, later in Russia and in Turkey where he was in charge of a field hospital. On his return to Berlin, he worked in Oppenheim-Cassirer's outpatient department, and in 1926 he became head of the department of neurology at the Second Medical Clinic of the Charité Hospital of the University of Berlin. He held the position of associate professor. In 1930 he became director of the Neurological Institute of Berlin, which he directed until the advent of the Nazi regime in 1933. At that time he was clinical professor of neurology at the University of Berlin.

In 1933 Dr. Lewey went to England where he worked in the department of occupational diseases of the nervous system of the British Home Office for one year. He was then invited by the late Dr. Frazier to join him at the University of Pennsylvania, where he became a visiting professor of neurophysiology and consultant in neurosurgery to the University of Pennsylvania Hospital. During World War II Dr. Lewey considered it his duty to join the armed services, and he became chief of neurology at the Cushing General Hospital in Framingham, Massachusetts, with the rank of lieutenant colonel. There he directed important studies on peripheral nerve injuries. On his return to the University of Pennsylvania Hospital he continued these studies at the peripheral nerve study center, and became professor of neuroanatomy in the Graduate School of Medicine and associate professor of neuropathology in the undergraduate Medical School of the University of Pennsylvania. He was also a consultant to the Commonwealth of Pennsylvania in occupational diseases of the peripheral nervous system and a diplomate of the American Board of Neurology and Psychiatry.

Dr. Lewey was one of the few neurologists equally well versed in the basic sciences and in clinical neurology. His research activities embraced the medullary centers of the eighth nerve; histopathologic studies, particularly the influence of various toxins; experimental studies on the cerebellum, the hypothalamus and on action potentials in the central nervous system. He was one of the first in Europe to use the stereotaxic method on experimental animals. In his clinical work he became particularly interested in chronaxie measurements. He applied this method successfully to the study of trigeminal neuralgia when he became an associate of Frazier, and later of Grant, and had an opportunity to analyze the enormous material of these neurosurgeons. His conclusions that there may be a central factor in the pathogenesis of trigeminal neuralgia has not yet found the recognition that it deserves. He also applied his chronaxie studies to vitamin deficiencies. However, his vision went beyond these special studies; he attempted to understand the patient's personality as a whole as evidenced by his book, *The Biology of the Personality*. His masterwork remains his book on *Tonus and Movement* which is based on careful clinical, neurophysiologic and histopathologic studies of a

large number of cases of paralysis agitans. He demonstrated that the histopathologic changes in this disease are widespread in the central nervous system and include not only the extrapyramidal system but also vegetative centers in the hypothalamus. In his most recent studies, he was interested in the application of the silver impregnation methods of the Spanish school to the study and differentiation of tumors.

Dr. Lewey obtained from his colleagues the recognition he deserved. He held the important position of secretary of the German Neurologic Association until his departure from Germany. In this country, he soon became a member of the American Neurological Association, the American Association of Neuropathologists of which he was vice president in 1938, the American Physiological Society and the Association for Research in Nervous and Mental Diseases. The International Hospital Association appointed him chairman of its neurologic section in 1931. He was intensely interested in the founding of the American Academy of Neurology and was chairman of its Board of Trustees. The Argentine Society of Normal and Pathological Anatomy made him corresponding member, and the Argentine Society of Neurology, Psychiatry and Neurosurgery made him an honorary member. He was also a fellow of the American College of Physicians and the College of Physicians of Philadelphia, a fellow of the American Medical Association and a member of the Philadelphia Neurological and Physiological Societies.

He was fortunate not only in his professional career but also in his private life. In the former Flora Maier, whom he married in 1924, he had a helpful and understanding companion.

E. A. SPIEGEL, M.D.

PROGRAM OF THE
AMERICAN ACADEMY OF NEUROLOGY
Second Biennial Meeting
April 11, 12, 13, 1951

CAVALIER HOTEL — VIRGINIA BEACH, VIRGINIA

An intensive review course in neuropathology will precede the meeting proper on April 9 and 10. Sessions will be held each day from 9 a.m. to 12 noon, and from 1 p.m. to 5 p.m., with evenings devoted to a projectoscope review of slides. The course will be conducted by A. B. Baker, M.D., A. L. Sahs, M.D., Fae Y. Tichy, M.D., A. Theodore Steegmann, M.D., Webb Haymaker, M.D., Francis M. Forster, M.D. and Maynard M. Cohen, M.D. Registration for the meeting starts April 10 at 5 p.m.

WEDNESDAY, APRIL 11, 1951

Morning Session 10:00 a.m.
Robert Wartenberg, M.D., *Presiding*
Gene Gordon, M.D., *Secretary*

Environmental Studies in Multiple Sclerosis
Gabriel Steiner, M.D., Detroit, Michigan

Trauma and Multiple Sclerosis
David J. Flicker, M.D., Cincinnati, Ohio

Early Recognition and Treatment of Multiple Sclerosis
I. Mark Scheinker, M.D., Cincinnati, Ohio

Modification of Symptoms in Multiple Sclerosis through the Use of Tetraethylammonium Chloride
Guy H. Williams, Jr., M.D., L. J. Karnosh, M.D., and Howard J. Tucker, M.D., Cleveland, Ohio

Generalized Arachnoiditis Following Spinal Anesthesia
N. W. Winkelman, M.D., Philadelphia, Pennsylvania

Neurologic Manifestations Following Spinal Anesthesia in Three Cases of Intraspinal Tumor
Jost J. Michelson, M.D., Boston, Massachusetts

The Pattern of Sensory Return in Partial and Recovering Spinal Cord Lesions
Benjamin Boshes, M.D., Meyer Brown, M.D., and Richard L. Crouch, M.D., Chicago, Illinois

The Face-Hand Test as a Diagnostic Sign of Disease of the Brain
Max Fink, M.D., Martin Green, M.D., and Morris B. Bender, M.D., New York City

WEDNESDAY, APRIL 11, 1951

Afternoon Session 2:00 p.m.
Benjamin Simon, M.D., *Presiding*
Henry V. Guhleman, Jr., M.D., *Secretary*

Analysis of the Various Methods of Treatment for Intractable Pain
David Cleveland, M.D., Milwaukee, Wisconsin

Clinical Observations on the Use of Benadryl for the Symptomatic Relief of Thalamic Pain
Ralph W. Barris, M.D., Los Angeles, California

Clinical Studies in the Therapy of Parkinsonism with Antihistamine and Antispasmodic Compounds
Abraham S. Effron, M.D., Paterson, New Jersey

Current Treatment in the Three Types of Parkinsonism
Lewis J. Doshay, M.D., Ph.D., and Kate Constable, M.D., New York City

The Catabolic Effects of Trauma to the Spinal Cord and Its Investigative Treatment with Testosterone Proprionate
Irving S. Cooper, M.D., Edward H. Rynearson, M.D., and Collin S. MacCarty, M.D., Rochester, Minnesota

Retraining Patients with Brain Damage
Joe R. Brown, M.D., Rochester, Minnesota

Failures in Migraine Therapy
Arnold Friedman, M.D., and Theodore J. C. von Storch, M.D., New York City

Carotid Jugular Anastomosis in the Child and Adult; Results of Treatment of Cerebral Spastics and Cerebral Thrombosis
Averill Stowell, M.D., and Robert A. Hayne, M.D., Tulsa, Oklahoma

Observations on the Effect of Electroshock Therapy in Two Neurologic Cases
Morton M. Stern, M.D., Newark, New Jersey

The Effect of Streptomycin on Tuberculous Meningitis: A Study of Four Cases at Necropsy
Martin G. Netsky, M.D., Nathaniel S. Ritter, M.D., and H. M. Zimmerman, M.D., New York City

THURSDAY, APRIL 12, 1951

Morning Session 10:00 a.m.
Roland Mackay, M.D., *Presiding*
John B. Pfeiffer, Jr., M.D., *Secretary*

Cerebral Fat Embolism
A. Silverstein, M.D.

Paraplegia in Flexion of Cerebral Origin
Paul I. Yakovlev, M.D., Middletown, Connecticut

Gonyalgia Paresthetica
Robert Wartenberg, M.D., San Francisco, California

Neuromyelitis Optica (Devic's Disease) Complicated by Spinal Adhesive Arachnoiditis and Block
Howard D. McIntyre, M.D., and Aurelia P. McIntyre, M.D., Cincinnati, Ohio

The Neuropathology of Post-Erythroblastotic Cerebral Sclerosis
John A. Wagner, M.D., and Milton S. Sacks, M.D., Baltimore, Maryland

The Central Nervous System in Disseminated Lupus Erythematosus
A. L. Sahs, M.D., E. C. Clark, M.D., and A. T. Coffee, M.D., Iowa City, Iowa

No Afternoon Session

FRIDAY, APRIL 13, 1951

Morning Session 10:00 a.m.
Paul F. A. Hoefer, M.D., *Presiding*
Sidney Cohen, M.D., *Secretary*

The Problem of Brain Damage in Shock Therapy
Lothar B. Kalinowsky, M.D., New York City

Alterations of Basal Ganglia Tremor During Sleep
Walter J. Friedlander, M.D., San Francisco, California

Clinical Diagnosis of "Stroke"; Value of Arteriography
Irwin Perlmutter, M.D., and Richard E. Strain, M.D., Miami, Florida

Dynamic (Serial) Electroencephalography in the Study of Vascular Lesions of the Brain
Ephraim Roseman, M.D., Richard P. Schmidt, M.D., Eldon L. Foltz, M.D., Louisville, Kentucky

What Neurology Has to Offer Child Guidance
Arthur R. Timme, M.D., Los Angeles, California

Psychologic Testing as an Aid in the Diagnosis of Organic Brain Disease
Edward D. Hoedemaker, M.D., and M. E. Mirriam Murray, M.S., Seattle, Washington

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Papers Read by Title

The Effects of Prostigmine in Primary Lateral Sclerosis
David J. Flicker, M.D.

The Brain Stem Reticular Formation, Its Relation to Brain Stem Seizures and Facial Spasms
Gerald F. Perry, M.D.

Chronic Anterior Horn Disease in Four Cases with an Excellent Clinical Recovery in Three Cases
Theodore T. Stone, M.D.

Friedreich's Ataxia, Associated with Myocardial Disorder in Five Siblings
Mabel G. Masten, M.D.

The Effects of ACTH on the Electroencephalogram
V. R. Zarling, M.D.

Some Histometabolic Aspects of Glia Cells in Various Neuropathologic Processes
Leon Roizen, M.D.

Spontaneous Carotid Artery Thrombosis
Madison H. Thomas, M.D.

Dysfunction of Autonomic Postural and Thermal Adaptation in Patients with Chronic Encephalopathy
Robert E. Litman, M.D.

Correlation of Biochemical Changes with Psychiatric States—100 Cases
Esther Somerfeld-Ziskind, M.D.

Diagnosis and Treatment of Brachial Plexus Injuries
Hugh W. Garol, M.D.

Metrazol in Narcosynthesis
Henry V. Agin, M.D.

Treatment of Herpes with Protamide
Russell T. Costello, M.D.

Hereditary (Family) Spastic Paraplegia
Gabriel A. Schwarz, M.D.

Spontaneous Subarachnoid Hemorrhage as a Manifestation of Cerebral Glioma
F. H. Hesser, M.D.

Joint Meeting of the
American Academy of Neurology
and the
American League Against Epilepsy

FRIDAY, APRIL 13, 1951

Afternoon Session 2:00 p.m.

William Lennox Testimonial Symposium on Focal Seizures

Focal Seizures in Children
Francis McNaughton, M.D.

Focal Seizures in Adults
Russell N. DeJong M.D.

Electroencephalographic Aspects of Focal Seizures
Herbert Jasper, M.D.

Neurosurgical Aspects of Focal Seizures
A. Earl Walker, M.D.

The American League Against Epilepsy invites registrants to remain and attend the League's sessions on Saturday, April 14.

Neurology

.....BOOK REVIEWS....

Physiology of the Nervous System

John Farquhar Fulton, M.D., Sterling Professor of Physiology, Yale University. Third edition, 1949. New York: Oxford University Press, 667 pages, $10.00.

The first edition of Dr. Fulton's book appeared in 1938, and since then it has served as a handbook of function of the nervous system. In 1943 a considerably amplified second edition appeared. The third for the most part brings up to date the facts presented in previous editions. Chapter arrangement of the book is unaltered and in this regard the only outstanding innovation is a change in nomenclature of the twenty-second chapter from "Cerebral Cortex: The Frontal Association Areas" to "The Orbital Frontal and Cingulate Regions." Those chapters dealing with physiology of sensory endings, peripheral nerves and spinal cord reflexes are essentially unchanged except for the addition of recently acquired facts, for example the studies of Weddell on causalgia and its explanation as due to an abnormal reduction of nerve nets.

Strong arguments for the chemical transmission of nerve impulses by acetylcholine are still maintained in this edition. The chapter on hypothalamus has been considerably elaborated, with much attention given to the studies on Verney on osmoreceptors. In the chapter on thalamus, important observations of the Montreal group on thalamic reticular systems and on cortical thalamic interrelations are discussed in detail. In the chapter on cytoarchitecture, evidence for cortical representation of the pyramidal system is presented in its newer light. Although Bonin and Bailey's observations on cortical architecture are not as yet complete for the primate series, their influence is felt in this third edition. It is to be expected that in future editions of this book the impact of these fundamental observations of Bonin and Bailey will be even more obvious. The anatomic-physiological studies on the buried cortex of the sylvian fissures in various species are well presented, as is the evidence for secondary sensory and motor areas.

In this new edition pros and cons of the argument regarding cortical representations of muscle versus movement are presented in considerable detail. The philosophical arguments for representations of movement are well set aside. The renamed chapter twenty-two, dealing with orbital frontal and cingulate regions, has been redone almost completely. It includes salient material of the monograph of the Association for Research in Nervous and Mental Diseases on the frontal lobes as well as the important facts of Dr. Fulton's own monograph on the frontal lobes.

In the chapter on extrapyramidal motor system new facts regarding the suppressor system are detailed and the suppressor functions of forebrain, cerebellum and reticular substance are described. The chapter on cerebellum includes new data on localization in both motor and sensory fields. Fulton has been much impressed by the work of Nulsen showing that variations of stimulation frequency, duration and intensity might alter facilitations and inhibitions.

One is somewhat disappointed to find that the role of the temporal lobe in psychomotor epilepsy, as shown by the work of Gibbs and his colleagues, is not mentioned. Since Fulton's book is largely concerned with studies on infrahuman primates, it is not surprising that the sphere of language functions and dysfunctions is not considered extensively. It is a little disappointing, however, to find that the only reference to alexia alludes to area 19, and the more important area 39 is not mentioned in this regard. This new edition of Dr. Fulton's book has been anticipated by men in many fields of medicine, but in no field as avidly as in clinical neurology. A succinct correlation of multiple data and varied observations by an extremely well informed and totally nonbiased experimenter and teacher is always welcomed, especially when this happens in a field as difficult as neurophysiology. Dr. Fulton's book remains the handbook for all men interested in the function of the central nervous system.

F. M. F.

Acute Head Injury

Joseph P. Evans, M.D., Associate Professor of Surgery, University of Cincinnati. 1950. Springfield, Illinois: Charles C Thomas, Publisher, 116 pages, $2.25.

This monograph describes the current views of the theory and treatment of the acute phase of head injury. After an introductory section on the handling of scalp wounds, the author discusses skull fractures and their complications. Meningeal hemorrhages are presented with particular emphasis on the compressive effect of clot upon cerebral physiology. In the chapter on cerebral trauma this factor is elaborated still further. Compression of the brain stem due to dislocation of the medial part of the temporal lobe through the incisura is shown to effect profound changes in cerebral function, even inducing a vegetative existence.

A conservative viewpoint is presented in the treatment of brain injury. Adequate oxygenation is rightly stressed. Excessive dehydration, the use of hypertonic solutions and routine lumbar drainage are decried. The author believes that surgical procedures have a limited role in the treatment of cerebral injuries per se.

The monograph gives a general, although not critical, review of present ideas on acute head injuries without entering into controversial issues. Some 24 appropriate illustrations and a selected bibliography supplement the text.

The reviewer is disappointed that the author considered a discussion of convalescence from a head injury beyond the scope of his assignment. With modern methods of tiding patients over the acute phase of craniocerebral injuries becoming so effective, the restitution and rehabilitation of the patient in society has assumed great importance.

A. E. W.

NEWSLETTER

MARCH, 1951

A. B. Baker, President
Pearce Bailey, President-Elect
Howard D. Fabing, Vice-President
Joe R. Brown, Secretary-Treasurer

AMERICAN ACADEMY OF NEUROLOGY

Scheele to Address AAN at Virginia Beach Dr. Leonard A. Scheele, Surgeon-General of the U.S. Public Health Service, is scheduled to give an address at the second biennial meeting of the American Academy of Neurology at Virginia Beach (April 11-13). The title of Surgeon-General Scheele's address is not definitely determined but he has intimated it will deal with the organization of the National Institutes of Health of the U.S. Public Health Service, with special reference to the newly established National Institute of Neurological Diseases and Blindness.

AAN Program All-inclusive The program committee promises an all-inclusive meeting. Besides the carefully planned scientific sessions of papers, exhibits and motion pictures, there will be a presidential address by A. B. Baker and an entertainment and recreational program which will provide a cocktail party, banquet, dancing, tours, and tournaments in golf, tennis and bridge.

Critical Dates of Meeting The critical dates of the meeting are: Monday, April 9, the intensive review course in neuropathology starts; Tuesday, April 10, registration for the AAN meeting begins at 5 p.m.; Wednesday morning, April 11, the scientific session opens; Friday afternoon, April 13, there will be a joint meeting of AAN with American League Against Epilepsy in a testimonial symposium to William G. Lennox on focal seizures. The AAN meeting adjourns officially at 5:00 p.m., Friday, April 13, but all AAN members and their wives are invited to the League cocktail party on Friday evening, and to their sessions on Saturday, April 14.

Make Reservations Now Program chairman Dave B. Ruskin announces that those who have not made reservations should do so immediately by writing directly to the Cavalier Hotel, Virginia Beach, Va. Reservations at the Cavalier are on the American plan, but European plan accommodations can be obtained within two blocks by requesting European plan reservations when writing to the Cavalier.

Critchley Coming to Virginia Beach Macdonald Critchley, dean of the Institute of Neurology, The National Hospital, London, will visit the U.S. to attend the Academy and Epilepsy League meetings at Virginia Beach. After the meetings he will give a series of lectures in California.

Program of Women's Auxiliary The Women's Auxiliary has organized a spirited campaign to contribute to the social activities at Virginia Beach. The social committee has formed a special group of fifteen members under Mrs. F. M. For-

ster, whose job it will be to assist those attending to become better acquainted during the lighter moments of the meeting. To further these efforts Mrs. F. O. Meister, secretary of the auxiliary, invites the ladies of Academy members to join the auxiliary and attend the Virginia Beach meeting. Any wife, mother, sister, adult daughter or adult granddaughter of a member in good standing is eligible for membership. The dues are $2.00 a year. Applicants may write to Mrs. A. L. Sahs, 600 Brookland Park Drive, Iowa City, Iowa, or register during the 1951 meeting.

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NANDBC Holds Second Meeting The National Institute of Neurological Diseases and Blindness Council had its second meeting in Washington, Feb. 16. The first meeting of this council was held Nov. 16, 1950 (See Newsletter, Vol. 3, No. 1, Jan. 1951). The next meeting probably will take place early in June....The establishment on firm ground of the National Institute of Neurological Diseases and Blindness (NINDB) still remains a problem for the future. Its internal organization is not fully determined nor has it been awarded any specific appropriation by Congress....Since this institute promises to be the major governmental source for neurologic research and training grants, it is essential that it receive aggressive support from all neurologists. All neurologic departments having a justifiable need for research grants, research fellowships or training grants in neurology should make the necessary applications. Requests for research grants or research fellowships should be forwarded to Dr. John C. Eberhart, Acting Chief, Research Grants Branch of the National Institute of Neurological Diseases and Blindness, National Institute of Mental Health, Public Health Service, Bethesda, Md. Applications for training grants should be forwarded to Dr. Seymour D. Vestermark, Acting Chief of Training Branch, National Institute of Neurological Diseases and Blindness, at the same address....Applications for grants are received at any time and are reviewed three times a year....

Howard Fabing Back from Korea Howard D. Fabing, AAN vice-president, recently returned from a trip to the Far East as a consultant to the Surgeon-General. His trip included visits to hospital installations in Hawaii, Okinawa, Japan and Korea, from Seoul to Pusan. Fabing commends the work of the medical corps in Korea in spite of a shortage of medical personnel, particularly of well-trained specialists, including neurologists. He was intrigued by the efficiency of the Swedish U. N. Hospital in Pusan, where "a G.I. Joe was just as happy to be a patient as in one of his own hospitals." The problem of staffing this hospital was resolved by a unique rotation policy, whereby the services of highly qualified civilian specialists were obtained on a contractual basis. According to the terms of the contract each specialist is given a tour of duty in Korea, not to exceed six months. This limit on duration of service enables the specialist to contribute to the war effort without fear of having his practice at home disrupted.

Annual Course in Clinical Neurology at Minnesota The annual continuation course in clinical neurology took place at the Center for Continuation Study, University of Minnesota, Jan. 29-Feb. 10. Established in 1936 as the first institution of its kind in the country, this continuation study center is a self-contained residence college on the university campus, devoting itself to short special courses in many fields, including clinical neurology. Living and working together under the same roof the neurologic student group is enabled to enjoy the full concentration and intimate interchange provided by a campus setting. The faculty for the session was drawn mostly from A. B. Baker's neurologic department at the University of Minnesota, supplemented by visiting instructors. Among the visiting faculty this year were Joe R. Brown, Henry W. Woltman and S. B. Wortis. The John Black Johnston (1868-1939) lecture, an annual feature of the course, was given this year by Horace W. Magoun, professor, department of anatomy, University of California Medical Center, Los Angeles. His subject: "Wakefulness and Sleep."

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American Board Results As the result of examinations held in New York, Dec. 18-19, 1950, the American Board of Psychiatry and Neurology certified 20 candidates in neurology. Among these, 14 were certified in straight neurology, three in supplementary neurology and three in both neurology and psychiatry. The successful candidates in neurology were: Sidney Berman, New Haven; R. G. Berry, Bethesda; Gustave G. Gordon, Brooklyn; W. V. Huber, San Antonio; C. A. Kane, New York; J. W. Kemble, Washington; E. C. Kunkle, Durham; R. L. Lam, St. Louis; Tiffany Lawyer, Jr., New York; Theodore Lipin, New York; Marian M. Millitzer, Long Beach, Calif.; Morton Nathanson, New York; E. Douglas Rooke, Mayo Clinic; and W. W. Wilson, Philadelphia. Those certified in supplementary neurology were: L. D. Boshes, Chicago; Leo Madow, Philadelphia; and C. W. Umlauf, Philadelphia. Those certified in both psychiatry and neurology: Kalman Frankel, Philadelphia; H. H. Pennes, New York; and Herta Seidemann, New York....The first Board examination in 1951 is scheduled for June 11 and 12 at Philadelphia....

ARNMD Elects New Officers At its 30th annual meeting in New York (Dec. 15-16,1950), the Association for Research in Nervous and Mental Disease elected the following officers for the year 1951: S. B. Wortis, pres.; J. C. Whitehorn, first vice-pres.; J. Lawrence Poole, second vice-pres.; Clarence C. Hare continues as sec.-treas. The 1951 meeting is scheduled tentatively to be held at the Roosevelt Hotel, Dec. 14-15, 1951. The subject for the 1951 meeting concerns the treatment of psychiatric disorders. Suggested subjects for the 1952 meeting are problems of consciousness and the chemistry of neuromuscular function. The secretary requests additional suggestions be forwarded by mail.

New Neurologic Motion Pictures Two new neurologic motion pictures have been produced by the Veterans Administration. The first, entitled "Seizure, the Medical Treatment and Social Problems of Epilepsy," is a 40 minute black and white sound

picture available on either 35 or 16 mm. film. It presents the newer medical and surgical diagnostic-treatment methods for epilepsy projected on a dramatic background story of the socio-economic obstacles encountered by an epileptic veteran. The second picture, "Introduction to Aphasia" is a 16 mm. color-sound film in three parts, each part having a running time of 30 minutes. It presents the problem of aphasia from the standpoints of cerebral localization, diagnosis and treatment through language retraining. The epilepsy film and the first part of the aphasia film will be presented at the Virginia Beach meeting. Requests for the use of these films on a loan basis should be sent to the VA Central Office Film Library, Court 5, South Building, U.S. Department of Agriculture, Washington 25, D.C. ...Sandoz Pharmaceuticals has produced a color sound film on the treatment of migraine for which Arnold Friedman was the technical advisor....

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Naval Neurology According to Captain George N. Raines, chief of psychiatry and neurology, U.S. Navy, present naval policy is to assign neurologists to neurologic units in naval stations. These units have an autonomous professional identity within the framework of a psychiatric service....Lt. Commander William Caveness of the N.Y. Neurological Institute operates such a unit in a naval hospital at Yokosuka, Japan....

Here and There The 1951 annual convention of the National Society for Crippled Children and Adults, 11 So. LaSalle Street, Chicago, will be held at the Palmer House, Chicago, Oct. 3-6....The National Paraplegic Foundation has a limited number of fellowships for research in spinal cord disorders. Information may be obtained from Dr. Leslie W. Freeman, director of surgical research, Indiana University School of Medicine, Indianapolis....The National Foundation for Infantile Paralysis, 120 Broadway, New York 5, announces the availability of a limited number of predoctoral and postdoctoral fellowships. ...The University of Kansas School of Medicine is offering a post-graduate course in applied neurology April 30 to May 3.... The Second International Poliomyelitis Conference will be held in Copenhagen, Denmark, Sept. 3-7....

Briefs The newly founded Spanish Society of Neurology has elected Henry Alsop Riley and Robert Wartenberg as honorary founder members and A. Earl Walker as an honorary member....The French Neurological Society (Societe francaise de Neurologie) has elected Pearce Bailey an honorary member....Jan Cammermeyer, neuropathologist at the University of Oslo, has arrived in the U. S. to become the VA neuropathologist on Webb Haymaker's staff at the Armed Forces Institute of Pathology....Sigwald Refsum, professor of neurology at the University of Bergen, Norway, is studying American methods in neurology at the University of Minnesota....

Pearce Bailey

Emotions and Clinical Medicine

Stanley Cobb, M.D. 1950. New York: W. W. Norton & Company, 243 pages, $3.00.

The title of this book is carefully and aptly chosen. The author does not attempt to discuss the whole field of emotion but only that aspect of it which he as a clinician has studied for many years. There is, accordingly, no waste movement and the discussion gets to the point immediately.

It is impressive to find the first chapter devoted to a clear and distinct idea of what emotion is. This is the work of John R. Reid, professor of philosophy at Stanford University, and is entitled, "Introduction: Semantics and Definitions." Finding that "it is all too common at psychiatric meetings to take sides on hopelessly ill-defined issues," he discreetly suggests that psychiatrists in their professional discourse, "take seriously the necessary logical conditions of communication and verification and keep constantly in mind the crucial role of definition in this process." The result of this reassertion of the great scholastic principle of defining terms before using them is that throughout the work the reader has the pleasant experience of feeling that the author knows what he is talking about.

The reader should not be deceived by the attractively small size of the book; it is not a book merely for casual reading. It repays close study. The chapters on the anatomy of the nervous system concerned with emotion are not written down or oversimplified, and there is concern for accuracy. A studious attitude on the part of the reader is both warranted and profitable. This is true in equal measure of the chapters on physiology and endocrinology.

The integration of all this basic material with the patient in the clinic is the motif of the remainder of the book. An extensive example of this process is the timely and detailed discussion of anorexia nervosa and its place in the scheme of clinical entities. Presenting combined emotional and physical causative factors, the seriousness of this disorder is emphasized by the fact that in the author's series four out of 16 patients died within four years of the beginning of the study. Perhaps a tinge of humor appears in the author's inclusion of the remarks of participants in the clinical conferences. These reflect some of the banalities that mask our confusion when forced with the necessity of coming to a conclusion but which somehow help to carry us onward through the maze of unknowns.

There is a critical appraisal of the practical value of the personality profile in patients with various diseases. It is here that the balanced clinical experience of many years comes to the fore with its ability to include large numbers of cases followed for a considerable portion of a lifetime. Cobb concludes that there is "a good deal in these observations" but that "the method has led to hasty and incorrect conclusions about some matters." Cobb states further "the method is literary, at best clinically descriptive . . . It is liable to abuse by investigators who are quick, intuitive and verbally plausible."

The book then is a well planned, well written discussion of the basic anatomic, physiologic and psychiatric data involved in emotion, brought up to date, and presented with seasoned clinical judgment.

A. R. V.

Carbon Dioxide Therapy—A Neurophysiological Treatment of Nervous Disorders

L. J. Meduna, M.D. 1950. Springfield, Illinois: Charles C Thomas, Publisher, 236 pages, $5.00.

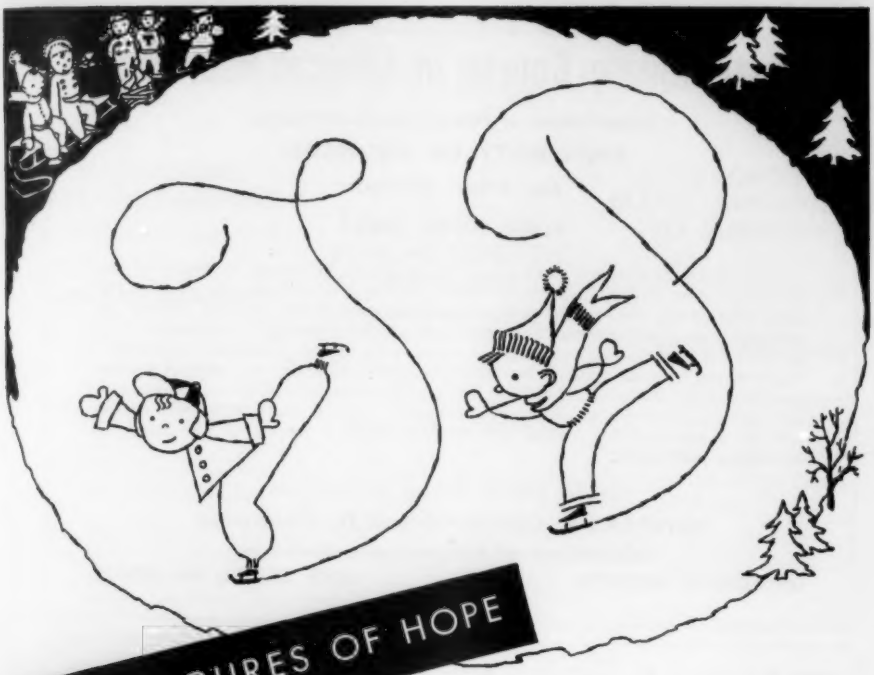
The distinguished propounder of metrazol convulsive therapy of schizophrenia, which during the late '30's and prior to electroshock therapy came to occupy a prominent place in the arsenal of the physical means of psychiatry, now brings forth a new method of treatment of psychoneurosis and of psychosomatic disorder by means of repeated inhalations of a mixture of 30 per cent carbon dioxide and 70 per cent oxygen.

Many will disagree with Dr. Meduna that "that which is true for one nerve cell, is true with respect to the aggregate of nerve cells, the whole brain." Many will disagree with many other theoretical propositions of the author. Few will, however, hold ill feelings toward him on this account. The book is written with candid enthusiasm and an unbounded faith in the universal validity of the principle that only by doing something to the patient is it possible to accomplish anything for him.

In the first three chapters of the book, the author discusses the central action of carbon dioxide, its effect upon the function of isolated nerve and upon the brain. In the fourth chapter, he discusses the technique of administration of the carbon dioxide treatment and describes behavioral phenomena and psychic states experienced by the patients under treatment. In a 100 page long fifth chapter, he gives a detailed account of illustrative case records, quoting mostly verbatim and at length the protocols of psychological tests and the voluble accounts of subjective experiences of the patients before, during, and after the treatment. In this reviewer's opinion, all this material, interesting as it is, could have been more convincing if it were more concisely presented. In a brief sixth chapter, the author argues the issue that "the phenomena accompanying the CO_2 narcosis are not, per se, due to autosuggestion," but that "the explanation of the improvements accomplished by the CO_2 treatment must rest upon the known physiological effects of the gas on the isolated nerve cell and upon the logical assumption that structures and organizations in the intact brain are susceptible to these same physiological effects of the gas." In the concluding chapter, he discusses what he calls "a neurophysiological theory of psychoneurosis" based on the concept of the reverberating circuits and of the so-called "feed back" principle in the mechanical assembly of the nervous system.

The author's material includes 100 cases of psychoneurosis and of psychosomatic disorders (other than obsessive-compulsive neurosis) classified according to his own "neurophysiological theory." Theoretic postulates of and frame of reference in which this classification is conceived do not lend themselves for a brief review and can be appraised only in the context of the whole book. The book abounds in debatable but suggestive ideas and should be of interest especially to psychiatrists. The method of Dr. Meduna carries apparently no particular risks to the patient. The reader may wish that the factual and theoretic material of the book were more judiciously organized.

P. I. Y.



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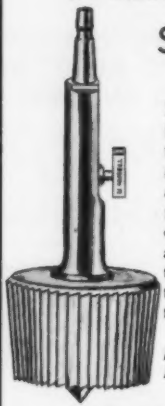

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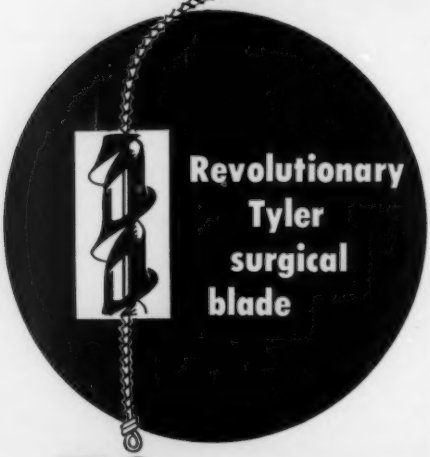

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The management regimen should include:[1]

I. Good physical and mental hygiene.
   a) Wholesome diet; Regular bowel habits; Avoid noxious materials, e.g. alcoholics; Moderate physical activity.
   b) Help overcome feeling that epilepsy is shameful; Encourage normal work and recreation; Regular sleep without overprotection.

II. Anticonvulsant medication selected on the basis of Exact Diagnosis:

"Certain drugs are more effective in one type of seizure than they are in another, and it is necessary to use proper drugs. The dosage must be individualized for each case."[1]

Thus, the best guide in selecting medication for a patient is the type of seizures present. (Frequently several drugs in combination is most effective.)

The table shows which drugs are indicated for each type of seizure. It will be noted that the newer hydantoin, Mesantoin, is effective for *grand mal*, Jacksonian and focal seizures.

MESANTOIN DOSAGE is adjusted to the lowest level adequate to attain freedom from seizures. Start with ½ or 1 tablet daily during the first week; increase the daily intake by ½ or 1 tablet during the next week. Continue this up to optimal dosage. When another drug has not given good results, Mesantoin is added by the same procedure; then the old drug is gradually reduced.

SIDE EFFECTS — Mesantoin produces side effects in some cases: Skin and blood changes are signs of sensitivity — the drug should be discontinued. Drowsiness develops upon reaching maximum dosage.

PRECAUTIONS — Certain precautions are necessary to minimize untoward effects.

a. close check on patient — repeated visits and blood counts.
b. No Mesantoin, if white cell count below 4000.
c. caution if (1) rash or blood changes.
   (2) History of drug sensitivity.
d. discontinue drug if (1) bleeding of gums or vagina.
   (2) Sore throat

TYPE OF EPILEPSY	PRIMARY CLINICAL MANIFESTATIONS	MEDICATION	AVERAGE ADULT DAILY DOSE★	LIMITING SIDE EFFECTS	SIGNS OF SENSITIVITY
GRAND MAL	Aura followed by loss of consciousness; tonic - clonic convulsions and autonomic disturbance, e.g., in bladder function.	Phenobarbital	1¼ grs. h.s. Usual max.: 3 grs. per day	Sleepiness	
		5,5 diphenyl hydantoin	1½ grs. t.i.d., p.c. Usual max. 6 grs. per day	Diplopia, staggering (may increase petit mal)	Overgrowth of gums, body hairs; itching rash on extremities, gastric irritation
JACKSONIAN	Convulsions begin in one area and spread outwards (Jacksonian march.). No loss of consciousness.[2]	3 methyl 5,5 phenylethyl hydantoin (mesantoin)	Adults: 2 to 6 tabs. Children: 1 to 4 tabs.	Sleepiness	Full details given; see Psychomotor cross-column below
		phenylacetylurea[3]	2 Gms. per day. Max. dose 6 Gms. per day[4]	Drowsiness[5]	Central nervous system affected, nausea, vomiting and abdominal pain[6]
PSYCHO MOTOR	Period of amnesia; actions apparently purposeful but mechanical; incoordination. Mild tonic spasms. In children: "behavior problems".[2]	3 methyl 5,5 phenylethyl hydantoin[4]	Adults: 2-6 tabs. Children: 1-4 tabs.	Pharyngitis, mucous membrane bleeding, lymphadenopathy, measles-like rash with itching and fever; in severe reaction: blood dyscrasia.	
		phenylacetylurea[5]	See phenylacetylurea—above		
PETIT MAL TRIAD	Attacks: in series (rapid succession), abrupt onset, few sec. duration; no aura nor impairment of consciousness. Rhythmic twitching (e.g. eyelids).	3,5,5 trimethyl oxazolidine 2,4 dione	0.9 to 1.2 Gms.	Inability to see in a bright light. Drowsiness	Hiccough, acneform rash, leukopenia
		N methyl derivative of phenobarbital	6 grs.	Sleepiness	

★Although an average daily dose can be stated for each of these drugs, to obtain best results it is necessary that the physician determine the dose required by each individual patient for maximum control of his seizures.

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"The relief of pain was superior to that obtained when using either pituitrin, thiamine chloride, autohemotherapy, sodium iodide or high voltage roentgen therapy. Further, vesicles and crusts disappear much more rapidly than in untreated cases.

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Additional clinical data on the dramatic results obtained with Protamide in the treatment of Herpes Zoster and the relief of the lightning pains and ataxia of Tabes Dorsalis will be furnished physician on request.

[1] *U.S. Armed Forces Med. Journal, September, 1950*

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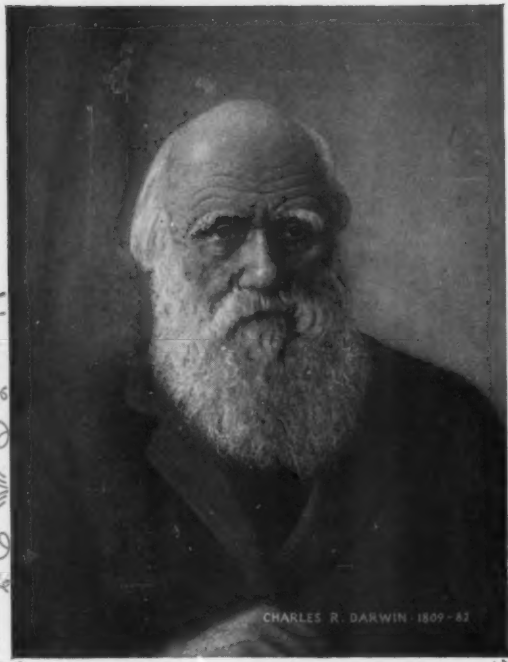

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